Baseline Oral Health Study

UnCoVer the Connections to General Health

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Clinical Study Protocol

Protocol No: CRO-2020-03-VERILY-LK

Version 4.0

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Protocol Signature Page

I, Principal Investigator, agree to conduct this study in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice (GCP), applicable legal and regulatory requirements, and in compliance with the provisions of this Protocol.

I am responsible for ensuring that the investigation is conducted according to this protocol and for protecting the rights, safety, and welfare of the research subjects. All personnel involved in the conduct of this study will complete Human Subject Protection training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

PRINCIPAL INVESTIGATOR

Principal Investigator	Signature	Date

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Version History

Version No., Version Date	Description
1.0, 14Apr2021	Initial Version
2.0, 10Nov2021	● Update to Figure 1 to include XRays and IMT/FMD timing (Section 1.3) ● Clarification of Inclusion and Exclusion criteria (Section 2.1) ● Clarification to Visit Schedule table (Section 3.2) ● Addition of X-Ray/Radiographs at S0 and T5 ● Clarification of IMT/FMD timing (ie. weeks) ● Administrative/Grammatical edits throughout the document
3.0, 23MAR2022	● Recruitment expanded to include the potential recruitment of participants from outside of Baseline Health Study (throughout) ● Stool kit clarified as optional (throughout) ● Inclusion criteria updated to remove CRP and CCS (Section 2.1) ● Exclusion criteria updated to include orthodontic treatment (Section 2.1) ● Removal of blinding language (Section 4.1) ● Adverse event reporting clarified to require only reporting of unexpected adverse events (AEs) (Section 11C) ● POCT-Q changed to apply only to treatment group (throughout) ● Administrative/grammatical edits throughout the document
4.0, 02May2023	● Remove branded commercial product naming (ex: “Colgate hum”) and update to more generic naming (throughout) ● Include subgroup of 50 participants where aMMP8 activity will be measured using rinse method ● Include “Peripheral Artery Disease (PAD)” in cardiovascular disease ● Update IMT and FMD measurements may occur before baseline and 8 weeks after the designated treatment visit

1. INTRODUCTION

1.1. Statement of the Problem

The most common oral diseases initiate as silent or asymptomatic (i.e. caries and periodontal disease) with very few outward signs of a problem until the tissue destruction becomes noticeable and irreversible for some conditions. There is a need to identify biomarkers to alert the population of their potential risk of having or developing these silent oral diseases. There is also a recognized association between the risk of developing oral inflammatory diseases for those with systemic inflammatory conditions (and vice versa). It has been shown that cardiovascular disease (CVD), diabetes, and periodontal disease are prevalent conditions in individuals throughout the United States and around the world. Higher CVD risk has been associated with severe chronic periodontal disease. Diabetes and periodontitis are considered complex chronic diseases with an established bidirectional relationship. For example, controlling gingival inflammation and periodontal disease is more difficult in people with uncontrolled or poorly controlled diabetes. Similarly, there is evidence that those presenting with oral inflammatory diseases are at higher risk for developing diabetes and more difficulty with glucose control, and they are at increased risk for cardiovascular disease. Thus, it has become critically relevant to identify more targeted technologies and clinical strategies aiming to reduce the oral inflammatory burden. The clinical research described in this proposal has been designed to better understand the biological pathways involved in the reported connections of oral to overall health and to identify biomarkers associated with oral health and disease.

The Baseline Oral Health Health Study is a randomized controlled trial to evaluate the impact of regular, professional non-surgical Intensive Periodontal Therapy (scaling and root planing and optimal oral hygiene with associated professional oral health behavior advice), on oral health as well as whether such effects are associated with corresponding changes to biomarkers characterizing systemic health. The study will be conducted in partnership with Verily and the Project Baseline Team, Colgate, and the University of North Carolina. The study population (ie. eligible participants) may be recruited from Project Baseline Health Study and the Baseline Community Study (ie.registry). Recruitment of participants may be expanded outside of the Project Baseline Health Study and the Baseline Community Study (ie. registry) as needed to support the study enrollment target. The Project Baseline Health Study is a longitudinal cohort study which characterizes participants across clinical, molecular, imaging, sensor, self-reported, behavioral, psychological, environmental, or other health-related measurements from onsite and/or remote visits, continuous monitoring through sensor technology, and regular engagement via an online portal, and mobile app. The purpose of the Baseline Community Study (ie. registry) is to build a community of volunteers that are interested in engaging in their health and/or contributing to clinical research. The data collected in this study may be used to develop tools and technologies in future exploratory studies and analysis of health and disease.

The study population to be recruited may include participants diagnosed with cardiovascular disease and/or type 2 diabetes mellitus (including prediabetes) and eligible for periodontal intervention. The

study will use dental centers and an experienced dental team to manage the oral care provided in this study.

1.2. Outcomes

Primary

- Impact of non-surgical periodontal treatment on oral health as measured by changes in periodontal probing depths
- Correlations between changes in periodontal health and changes in systemic health measures:
    - Glycated hemoglobin (HbA1c) (prediabetic and type 2 diabetic cohorts)
    - Flow-mediated dilation

Secondary

- Impact of treatment on other oral health measures:
    - Bleeding on probing
    - Clinical attachment level
    - Dental plaque index
    - Gingival index
- Impact of treatment on systemic health measures:
    - Flow-mediated dilation
    - Glycated hemoglobin (HbA1c) (prediabetic and type 2 diabetic cohorts)
    - Carotid intima media thickness (IMT)
    - High sensitivity C-reactive protein (hs-CRP) (all cohorts)
    - Lipid profile: Total cholesterol/LDL cholesterol/Triglycerides
- Impact of treatment on emotional (affectional) state and beliefs about disease as measured by PANAS and PMT surveys

Exploratory

- Prevalence and severity of periodontal disease in screen-eligible participants at initial oral health screening
- Relationship between treatment on all other molecular analytes, including protein, metabolite and immune system inflammatory biomarkers and subgingival plaque microbiome
- Correlations among all other oral and systemic health metrics
- Correlations among oral and systemic health metrics with molecular analytes, including inflammatory biomarkers and subgingival plaque microbiome.

1.3. Summary of Research Plan

The Baseline Oral Health Study will enroll approximately 200 participants in the study with approximately 100 participants each within the Control Group and the Treatment Group. The study population will be recruited from the Project Baseline Health Study participants in the North Carolina region and may be expanded to include subjects recruited outside of the Project Baseline Health Study if the initial screening from the Project Baseline Health Study pool of participants in the North Carolina region does not fulfill study enrollment powering. Screening methods for eligible participants may include review of electronic health records (EHR) or other systems in compliance with local requirements. The participants enrolled in the study will then be randomized into a Control Group and Treatment Group. The screened participants that become eligible and consented to this study will be seen at dental health sites. UNC study team will be the Principal Investigating team for this protocol.

The periodontal disease study will be presented to eligible participants and those interested will be scheduled for a screening visit (S0). (See Figure 1). At the screening visit, participants will be consented and provided with an oral health assessment, initial X-Ray series (Full Mouth series and vertical bitewings) per standard of care, a point of care blood glucose test and will be scheduled to receive Screening Visit flow mediated dilation (FMD) and carotid intima media thickness (IMT) measurements. Those meeting in/ex criteria will be enrolled into the study and a Screening Visit 1 (S1) will be scheduled for those subjects who need hopeless teeth extracted. A Screening Visit 2 (S2) may be scheduled as a post-operative visit or to extract additional hopeless teeth depending on allotted time available for the Screening Visit visit 1 (S1). The subjects will additionally be scheduled for the Baseline visit (T0, see Figure 1). The Screening Visits should be scheduled to take place no later than 2 weeks before the scheduled Baseline visit.

At the Baseline visit, another oral health assessment will be conducted, along with collection of biospecimen samples ie. blood, stool (optional), saliva, plaque, tongue biofilm, and gingival crevicular fluid. Subjects will then be randomized using a 1:1 protocol to a standard care group (Control Group) and a therapy group (Treatment Group). The Control Group will receive an initial periodontal treatment consisting of a pre-procedural rinse and scaling & root planing (SRP). Subjects in the Control group should refrain from non-study periodontal treatments for the duration of the study. The Treatment Group will receive the same periodontal treatment in addition to having subgingival chlorhexidine irrigation. All subjects will also complete a set of questionnaires (PANAS & PMT) using an online form. A subset of 50 subjects from each group will be randomly selected to have oral images captured using an intra-oral scanner at Baseline and a subset of follow-up visits. Subjects in the Treatment Group will receive a commercial connected toothbrush, a stannous fluoride toothpaste , mouthwash , proxabrush , and floss to be used at home along with instructions on their use. Brush heads for the connected toothbrush will be replaced every 3 months and products (toothpaste, mouthwash, proxabrush, and floss) will be replenished at every site visit. Additionally, subjects in the

Treatment Group will also receive brief behavioral advice from dental professionals focusing mainly on motivation and acknowledgement. Subjects in the Control Group will receive no products during the course of the study. They will receive Colgate products which may include a commercial connected toothbrush, toothpaste, mouthwash, proxabrush, and floss at the end of the study.

For a subgroup of 50 individuals, levels of active matrix metalloproteinase-8 (aMMP-8) will also be measured quantitatively using rapid point of care (PoC) chairside aMMP-8 kits (Periosafe®, Dentognostics GmbH, Solingen, Germany). The additional samples will be collected from 4 sites on a tooth with probing depth $\geq$ 5mm on the same visit as GCF samples will be collected.

Subjects will be scheduled to receive flow mediated dilation (FMD) and carotid intima media thickness (IMT) measurements prior to Baseline and approximately 8 weeks after their Baseline visit. Also in those visits, for a subset of 50 individuals aMMP8 activity will be measured using rinse method following manufacturer instructions and the chair side data positive aMMP-8 test is based on a cutoff of 25 ng aMMP-8 per milliliter of filtrate derived from 5 mL mouthrinse

Subjects in both the Control and Treatment Group will attend 3 follow-up visits (respectively T1-T3, see Figure 1). At these visits, the Control Group will have a clinical exam and a biospecimen collection while the Treatment Group will have a biospecimen collection followed by a clinical exam, periodontal treatment consisting of scaling and root planing and chlorhexidine preprocedural rinse and chlorhexidine irrigation (Chlorhexidine Gluconate Oral Rinse, 0.12%), and will be provided with new products to support the oral hygiene regimen. Finally, during follow-up visits, subjects in the Treatment Group will also receive specific behavioral advice focusing on monitoring their progress (through use of brushing data), motivation and reinforcement. Depending on the progress of each subject, IF-THEN plans designed to overcome barriers in using the oral hygiene regimen can be deployed. Dental professionals will be providing scripted and standardized advice to subjects to the Treatment Group. All subjects (control and therapy group) will also complete a set of questionnaires (PANAS & PMT) using an online form. FMD and IMT will also be measured (approximately 8 weeks after T2).

A fourth follow-up visit, (T4, see Figure 1) occurs at approximately Month 12 and at this visit, all subjects (regardless of group assignment) will receive a clinical exam, biospecimen collection, and periodontal treatment including subgingival chlorhexidine irrigation. At this visit, the treatment group will receive brief behavioral advice focusing on motivation and support and both groups will complete a set of questionnaires (PANAS & PMT) using an online form.

Participants will be scheduled to receive FMD and IMT measurements approximately 8 weeks after their T4 visit.

The final follow-up visit (T5, see Figure 1), occurs at approximately 15 months after the Baseline visit. Both groups will receive a clinical exam and biospecimen collection. At T5, a second X-Ray series will be taken for qualitative analysis as part of the research purposes. The Control Group will be asked to fill out a questionnaire on the oral care products they used during the study. They will receive Colgate products which includes a commercial connected toothbrush, toothpaste , mouthwash, proxabrush, and dental floss at the end of the study.

After completion of the study, participants will be recommended to continue treatment with their usual dentist or other local dental professional. Finally, all subjects will complete a set of questionnaires (PANAS & PMT) using an online form.

Subjects who have been randomly selected to receive intraoral scans at Baseline will also receive intraoral scans at T2, T4, and T5.

In between visits starting at the end of the face-to-face visit at T0 and ending after T4, Treatment Group subjects will also receive additional support via text messages. This support will aim on motivation and reinforcement in order to support the use of the oral hygiene regimen at home during the study and to assist with the creation of long-term habits around good oral hygiene practices.

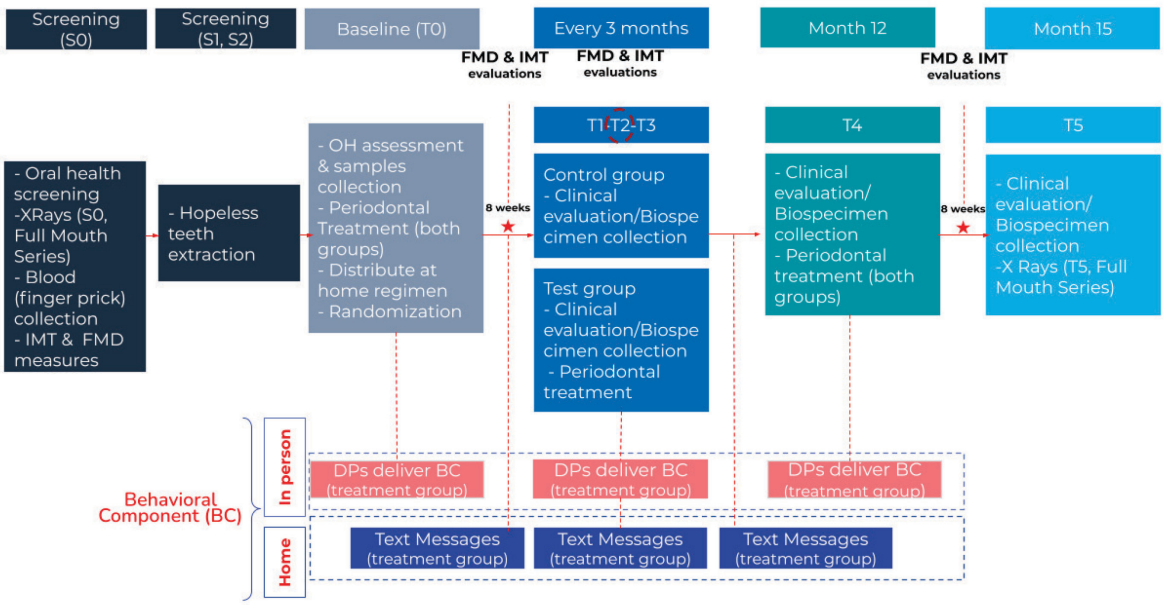

Figure 1: Clinical Design. Eligible subjects are screened at an initial screening visit (S0) and those meeting the in/ex criteria are enrolled and scheduled for 7 subsequent visits. Screening Visit visits (S1,S2) may be scheduled to extract hopeless teeth or to perform post-operative treatments as assessed during the screening visit S0 and as required to be eligible to be enrolled in the study. A Screening Visit visit will also be completed to take FMD and IMT measurements. At the Baseline visit (T0), a baseline oral health assessment will be conducted along with an initial periodontal treatment and randomization to Control or Treatment Groups. Subjects randomized to the Treatment Group will receive distributions of home regimen products. Four follow-up visits (T1-T4) will then take place approximately every three months. All subjects, irrespective of group assignment, will receive a second (and final) periodontal treatment at T4. The final visit (T5) will take place approximately 3 months after the cessation of treatment for both groups. Biospecimen will be collected for all 6 visits (T0-T5). Intra-oral scans for the selected subset of subjects will be captured at T0, T2, T4, and T5. Study will include two X-Rays (Full Mouth Series), to be taken at S0 (per standard of care) and at T5 for qualitative research purposes. *X-Rays (S0 Full Mouth Series) should be completed at the end of the screening phase during S0.

2. ELIGIBILITY AND ENROLLMENT

2.1. Eligibility Requirements

Inclusion criteria (AND):

- At least eighteen (18) years of age but not older than seventy (70) years of age at time of screening
- Able to speak and read English
- Has at least 16 teeth present.
- Able to consent, follow an outpatient protocol, and is available by telephone
- Has either moderate (stage II) or severe (stage III) periodontitis:
    - Stage II – Interdental clinical attachment level (CAL) at the site of greatest loss = 3 to 4mm with maximum probing depth ≤ 5mm
    - Stage III - Interdental CAL at the site of greatest loss ≥ 5mm, probing depth (PD)≥ 6mm, and radiographic bone loss (vertical bone loss ≥ 3mm)
- Has at least one of the following indicators of cardiometabolic disease in the following range:
    - Type 2 diabetes: 9% ≥ HbA1c ≥ 6.5% OR Prediabetes: 6.4% $\geq$ HbA1c $\geq$ 5.7% OR
    - CVD:
        - Medical history of Myocardial Infarction, Coronary Artery Disease, Peripheral Artery Disease (PAD) or stroke
- Access to iOS devices or Android devices with appropriate versions to be compatible with the applications to complete study procedures.
- Females of childbearing capacity must be willing to have pregnancy test

Exclusion criteria (OR):

- Individuals who exhibit gross oral pathology
- Presenting oral manifestations of systemic diseases (e.g. pemphigus, pemphigoid, lupus)
- Presence of any acute or chronic systemic infection as determined by the clinician
- Periodontal treatment performed within 6 months prior to study start
- Refusal to extract hopeless teeth identified as determined by the clinician at the screening visit.
- Participating in any other interventional cardiometabolic or Oral Health study
- Individuals currently undergoing any type of orthodontic treatment (e.g. aligners)

2.2. Urgent Treatment

After the subject has undergone the oral health assessment at the screening visit (S0, see Figure 1), an experienced study dentist will inform the subject of any urgent dental treatment needs such as endodontics, oral surgery, and restorative dentistry to be carried out prior to the baseline (T0) visit. In addition, the study dentist will make a determination of hopeless teeth. These teeth will be recommended for extraction in advance of the baseline (T0) visit.

If required, urgent treatments and hopeless teeth extraction will be completed between the date of the screening (S0) visit and no later than 2 weeks prior to the scheduled Baseline (T0) visit. Both the Screening Visit visit (S1) and an additional Screening Visit visit (S2), depending on allotted time available in S1, may be used for this purpose. Discretion is left to the study dentist as to whether or not the subject needs to revisit periodontal screening after urgent treatments are completed. Urgent treatments will not be provided within the study. Subjects will be informed of the urgent treatment needs.After completion of the study, participants will be recommended to continue treatment with their usual dentist or other local dental professional. During the treatment period (T1-T4), no periodontal disease progression is expected. In the Control Group, if any site demonstrates an increase in periodontal pocket depth $\geq$2mm, the specific tooth will be monitored to receive site-directed scaling and root planing.

For all subjects, during screening, the guidelines for determining “hopeless prognosis” and need for dental extractions are:

- Grade III mobility Untreatable Class III furcation involvements
- Teeth with periodontal attachment loss within 3 mm of the root apex
- Extensive crown or root caries.
- Clinical dental measures which include UNC Modified Plaque Index (Greene & Vermillion); Gingival Index (GI), Löe and Silness; bleeding on probing (BOP), probing depth and cementoenamel junction measures relative to the gingival margin (CEJ) on six sites for all teeth. Clinical attachment level (CAL) is calculated from the sum of probing depth and CEJ scores.
- Root fragments communicating with the oral environment
- Conditions preventing successful elimination of odontogenic infection

All periodontal assessments and treatment (both groups) will be conducted by periodontists, general dentists or dental hygienists listed as project personnel who are licensed, trained, calibrated and certified prior to the start of the study. This protocol specific training and calibration takes place at the UNC sites which includes standardization of screening procedures, clinical measurements, sample collection and treatment procedures including oral hygiene instructions.

2.3. Clinical Dental Measures

2.3.1. Clinical Periodontal Assessments

Clinical examiners will be calibrated prior to commencement of the study for training of study procedures and for documentation of acceptable intra- and inter-examiner measurement reliability. This examiner calibration and training is under a separate protocol. Clinical parameters will include the Gingival Index,

Plaque Index, pocket depth, bleeding on probing, and clinical attachment level. Clinical parameters will be measured using a manual University of North Carolina (UNC-12 or UNC-15) periodontal probe.

The gingival index will be scored on three facial surfaces (distofacial, facial, mesiofacial) and three lingual surfaces (distolingual, lingual, mesiolingual). Areas are examined by placing the periodontal probe under the gingival margin at approximately 1mm deep and sweeping the probe from the distal surface to the mesial surface in quadrants I and IV and mesial to the distal surface in quadrants II and III. After each quadrant is swept, calls are made based on gingival inflammation and the presence or absence of bleeding according to criteria which range from 0 to 3.

Modified Gingival Index (Löe & Silness)

- 0 = Normal gingiva
- 1 = Mild inflammation: slight change in color, slight edema. No bleeding on probing.
- 2 = Moderate inflammation: redness, edema, and glazing. Bleeding on probing.
- 3 = Severe inflammation: marked redness and edema. Ulceration. Tendency for spontaneous bleeding

UNC Modified Plaque Index (Greene & Vermillion)

Full mouth plaque assessment shall be assessed using the UNC Modified Plaque Index (Greene and Vermillion). Plaque scores shall be visually assessed at 6 sites per tooth (distobuccal, buccal, mesiobuccal and distolingual, lingual, mesiolingual surfaces) on a scale of 0-3.

- 0 =No debris or stain present on the clinical crown.
- 1 =Soft debris covering not more than 1/3 of the clinical crown (cervical 3rd), or presence of extrinsic stains without other debris regardless of surface area covered.
- 2 =Soft debris covering more than 1/3, but not more than 2/3 (middle 3rd) of the clinical crown.
- 3 =Soft debris covering more than 2/3 of the clinical crown

2.3.2. Biological Samples

After screening Visit (S0), serial fasting blood samples will be collected , Baseline (T0), and at each 3 month follow-up visit up until the last visit at 15 months (T1-T5). These blood samples will be assessed for hs-CRP, hemoglobin A1C, and fasting lipid profile in a blind fashion. They may also be used in LC/MS assays to quantitate blood proteins at each time point.

Biological Dental Specimens including Gingival Crevicular Fluid (GCF), dental plaque, tongue biofilm, and saliva will be collected at Baseline (T0), and at each 3 month follow-up visit until the last study visit (T1-T5). The subjects will also be asked to provide optional stool samples at Baseline (T0), T2, and T4.

Saliva and GCF will be collected for measuring inflammatory and endothelial protein biomarkers by high-sensitivity immunoassays. Plaque and tongue biofilm as well as stool samples will be stored for future analysis. Samples will be collected at each enrollment center and processed and analyzed at the center.

Biospecimen	**Volume**	**Timepoints**
Whole Blood	Approximately 40 ml *One drop from finger prick for A1c	S0*, T0, T1, T2, T3, T4, T5
Gingival Crevicular Fluid (GCF)	n/a	T0, T1, T2, T3, T4, T5
Dental Plaque	n/a	T0, T1, T2, T3, T4, T5
Tongue Biofilm	n/a	T0, T1, T2, T3, T4, T5
Stool (optional)	Approximately 500 mg	T0, T2, and T4
Saliva	Approximately 5 mL	T0, T1, T2, T3, T4, T5

2.3.3. Clinical Measures

Carotid IMT Measurement:

Carotid intima-media thickness (IMT): Subclinical atherosclerosis will be assessed by measuring carotid IMT. Longitudinal ultrasound images of the distal 1 cm segments of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries will be acquired. IMT will be measured as the distance between luminal-intimal interface and medial-adventitial interface. Mean IMT will be calculated as the average of all measurements; mean maximum IMT will be calculated as the average of maximum wall thicknesses for each of the regions.

Flow mediated dilation (FMD): Vascular endothelial function will be assessed by measuring flow-mediated dilation (FMD) of the brachial artery at Screening Visit, after baseline, 6 month follow-up, and 1-year follow-up. Ultrasound images of the right brachial artery and Doppler measures of arterial flow will be acquired before and after reactive hyperemia is induced by inflating a pneumatic occlusion cuff placed around the lower arm. FMD will be calculated as the percent change in arterial diameter from baseline. Peak hyperemic flow will be expressed as the time-velocity integral of the Doppler velocity .

*IMT and FMD measurements may occur before baseline and 8 weeks after the designated treatment visit.

2.4. Data from Project Baseline Health Study & Baseline Community Study

For participants enrolled from the Project Baseline Health Study and the Baseline Community Study (i.e. registry), data captured in the Project Baseline Health Study and the Baseline Community Study may also be used for the Baseline Oral Health Study.

For the purposes of screening and enrollment of participants outside of the Project Baseline Health Study and the Baseline Community Study (i.e. registry), this study may collect screening, baseline, demographic information and medical history data from the participant's medical record.

2.5. Patient Reported Outcomes and Questionnaires

2.5.1. Positive and Negative Affect Schedule (PANAS)

Developed by Watson & Tellegen (1988) the PANAS scales measure positive and negative affect using a 20-item survey with responses on a 5-point Likert scale (1: very slightly or not at all - 5: extremely). Positive and negative effects are both important variables for mood and overall psychological state. A number of mood questionnaires and scales have been developed to measure these two variables; however, many existing measures are inadequate, showing low reliability or poor convergent or discriminant validity. The PANAS scales bridge these gaps by providing reliable and valid Positive Affect and Negative Affect scales that are also brief and easy to administer. Both scales are shown to be highly internally consistent, largely uncorrelated, and stable at appropriate levels over a 2-month time period. The PANAS scales have been used extensively in clinical and health research. For this study, all subjects will complete the PANAS scales starting at T0 and finishing at T5. The scales will be administered and completed electronically.

2.5.2. Protection Motivation Theory (PMT) questionnaire

The PMT questionnaire was developed by Asimakopoulou et al. (2015) to measure patients' beliefs (cognitions) regarding periodontal disease, the treatment and management of disease over-time. Grounded in the Protection Motivation Theory approach (Rogers, 1975), the PMT questionnaire measures 7 beliefs (cognitions) relating to periodontal disease. More specifically, PMT measures: self-efficacy, threat, and coping appraisals and intention to change behavior. The PMT measure was scored using 7-point Likert scales (from 1: Not at all to 10: Extremely so). For this study, all subjects will complete the PMT questionnaire starting at T0 and finishing at T5. The scales will be administered and completed electronically.

2.5.3. Modified version of POCT-Q Questionnaire

The modified version of the POCT-Q addresses oral health perceptions and brushing habits. The instrument is related to the use of a connected connected toothbrush. It measures a range of patient experiences and behaviors related to the use of a connected toothbrush. For this study, all subjects in the Treatment group will complete the questionnaire at baseline (T0), 1 month after T0, T1, T4, 1 month after T4 and T5. The questionnaire will be administered and completed electronically.

2.6. Randomization

Subjects are randomized to the Treatment or Control group at the Baseline (T0) visit following the protocol described in the Statistical Analysis Plan.

3. PARTICIPANT FOLLOW-UP

3.1. Overview

All subjects enrolled in the Baseline Oral Health Health Study will report to the clinical facility having refrained from any oral hygiene procedures for **twelve** hours prior to their examination and having refrained from eating, drinking or using tobacco products, including chewing tobacco, for **twelve** hours prior to their examination. Subjects will be followed-up for cardiovascular, HbA1c and periodontal conditions. Follow-up contacts begin approximately 3 months after Baseline (T0) visit and will reoccur at approximately 6, 9, 12, and 15 months after Baseline (T0) visit. A contact window of plus or minus 28 days around each Follow-up visit's (T1-T5) target date is allowed. Follow-ups will include review of current medications, adverse events, cardiovascular endpoint inquiry and assessment, clinical data collection (blood pressure, heart rate, weight, and height), dental history since last contact, oral periodontal examination and indices, and sample collections (i.e. blood, saliva, dental plaque, tongue biofilm, GCF, and stool when applicable). All subjects will have an IMT and FMD analysis prior to Baseline and approximately 8 weeks after the Baseline (T0), Follow-up 2 (T2) , and Follow-up 4 (T4) visits.

3.2. Visit Schedule

Visit	Screening (S0)	Screening Visit 1-2[1] (S1-S2)	Baseline (T0)	Follow-up 1 (T1)	Follow-up 2 (T2)	Follow-up 3 (T3)	Follow-up 4 (T4)	Follow-up 5 (Final visit) (T5)
Timeline	-90 days	-89 to -14 days	0 day	90 days ± 28 days	180 days ± 28 days	270 days ± 28 days	360 days ± 28 days	450 day ± 28 days
Type of visit	Dental Clinic	Dental Clinic	Dental Clinic	Dental Clinic	Dental Clinic	Dental Clinic	Dental Clinic	Dental Clinic
Informed Consent	x							
Dental Screen	x							
Extractions[2]		x[2]						
Vitals	x	x	x	x	x	x	x	x
Medical History	x	x	x	x	x	x	x	x
Diet Questionnaire			x	x	x	x	x	x
PANAS			X (online)	X (online)	X (online)	X (online)	X (online)	X (online)
PMT			X (online)	X (online)	X (online)	X (online)	X (online)	X (online)
X-Ray Full Mouth Series	X							X
PreProcedural Rinse			x	x*	x*	x*	x	
Periodontal Exam	x		x	x	x	x	x	x
Dental CRFs	x	x	x	x	x	x	x	x
Biological Samples: Blood	x***		x	x	x	x	x	x

Biological Samples: GCF, [POC aMMP8 (subset)], saliva, plaque, tongue biofilm			x	x	x	x	x	x
Stool samples (optional)			x		x		x	
POC aMMP8 mouthrinse			x		x		x	
Carotid IMT Ultrasound	x		x		x		x	
Flow- Mediated Dilation	x		x		x		x	
Periodontal treatment			x	x*	x*	x*	x	
Intra-oral Scan (select subset)			x**		x**		x**	x**
Behavioral support (on site)			x*	x*	x*	x*	x*	
Review Brushing Data from Connected Brush			x*	x*	x*	x*	x*	x*
Distribute at-home regimen			x*	x*	x*	x*	x*	x

[1]Screening Visit (1-2) can span two days depending on the allotted time for extractions
[2]Extractions will occur as needed based on dental assessment
*Treatment group only
**For approximately 50 subjects from each of Control and Treatment groups
*** Blood sample - finger prick

Additional assessments would be conducted in addition to the above listed Schedule of Assessments. This may include:

- All participants within the Treatment group will complete the modified version of the POCT-Q at baseline (T0), 1 month after T0, T1, T4, 1 month after T4 and T5.
- The Baseline (T0) visit may expand over 2 days (if necessary at the discretion of the investigator)
- Behavioral support text messages will be provided to the Treatment group throughout the study.

3.3. Post-Baseline Visit Procedures

Participants will report to the clinical facility having refrained from any oral hygiene procedures for **twelve** hours prior to their examination and having refrained from eating, drinking or using tobacco products, including chewing tobacco, for **twelve** hours prior to their examination.

Post-Baseline evaluations will consist of:

Follow-up contacts begin 3 months after initial treatment visit or baseline visit and will occur again at approximately 6, 9, 12, and 15 months following periodontal intervention. A contact window of plus or minus 28 days around each target date is allowed.

Follow-ups will include review of current medications, adverse events, cardiovascular endpoint inquiry and assessment, clinical data collection (blood pressure, heart rate, weight, and height), dental history since last contact (including oral care regimen and products) and periodontal evaluation as well as biospecimens collection (saliva, blood, GCF, tongue biofilm, stool, and plaque samples).

All participants will be given (oral and written) instructions in basic oral hygiene. This will be provided by the study investigators and staff in collaboration with the subject's health care provider. Periodontal risk factors specifically targeted will include diabetes, use of tobacco products, including chewing tobacco, diet, exercise and body weight.

Blood Pressure (BP) will be recorded at each visit. Averaged consecutive triplicate readings (for IMT/FMD visits only) on the patient's left arm will be obtained with a BP monitor. For dental clinic visits, only one reading is necessary. Participants will rest for five minutes sitting in an upright position on the dental chair, after which BP recordings will be performed. Patients will rest for five minutes between blood pressure readings.

The POCT-Q will be measured for participants within the Treatment group at baseline (T0), 1 month after T0, T1, T4, 1 month after T4 and T5.

Carotid intima-media thickness (IMT): Subclinical atherosclerosis will be assessed by measuring carotid IMT at baseline and at a one-year follow-up visit. Longitudinal ultrasound images of the distal 1 cm segments of the right and left common carotid arteries, carotid bulbs, and internal carotid arteries will be acquired. IMT will be measured as the distance between luminal-intimal interface and medial-adventitial interface. Mean IMT will be calculated as the average of all measurements; mean maximum IMT will be calculated as the average of maximum wall thicknesses for each of the regions.Flow Mediated Dilation(FMD): Vascular endothelial function will be assessed by measuring flow-mediated dilation (FMD) of the brachial artery at baseline, 6 month follow-up, and 1-year follow-up. Ultrasound images of the right brachial artery and Doppler measures of arterial flow will be acquired before and after reactive hyperemia is induced by inflating a pneumatic occlusion cuff placed around the lower arm. FMD will be calculated as the percent change in arterial diameter from baseline. Peak hyperemic flow will be expressed as the time-velocity integral of the Doppler velocity envelope obtained immediately following cuff release.

3.4. Treatment Dental Procedures

The goal of this treatment would be to keep bleeding scores <20%. The subjects in the Treatment Group will be re-examined at follow-up visit 1-5 and receive supportive maintenance care consisting of scaling and root planing and chlorhexidine irrigation. Subjects in the Control Group will receive scaling and root planing therapy at Baseline and scaling and root planing therapy with chlorhexidine irrigation at Visit 4 (12 months after Baseline). Thus, during the treatment period, bleeding on probing scores and probing measurements will be monitored to measure the efficacy of the treatment and assure safety.

All periodontal assessments and treatment (both groups) will be conducted by periodontists, dentists or dental hygienists listed as project personnel who are licensed, trained, calibrated and certified prior to the start of the study. This protocol-specific training and calibration takes place at the UNC site, which includes not only standardization of clinical measurement, but also treatment procedures.

4. PERIODONTAL INTERVENTION

4.1. Overview

Subjects who signed a consent form and met the inclusion criteria at the screening examination will have been enrolled in the study and randomized to one of two groups.

This section of the Baseline Oral Health Health Study addresses procedures related to the periodontal intervention provided for the patients randomized into the two different groups.

Periodontal treatment throughout the Study will be provided only by experienced general dentists, periodontists or dental hygienists who are licensed, trained and calibrated prior to the start of the study.

Overview of Treatment Therapy

At the Baseline visit, both the Treatment and Control Groups will receive an initial standard cycle of scaling and root planing after subgingival plaque removal.

The Treatment Group will receive five sessions of full-mouth intensive removal of subgingival dental plaque biofilms with the use of scaling and root planing after the administration of local anesthesia (2% xylocaine with epinephrine 1:100,000 or alternative). Emphasis will be on thorough debridement to achieve complete removal of calculus from infected root surfaces, particularly at sites with furcation involvement. Treatment will be carried out using Cavitron Ultrasonic Scalers and handheld dental curettes. Hopeless teeth will be extracted, and Chlorhexidine will be delivered locally.

4.2. Staff for Treatment

Dental operators who are licensed, experienced and study-trained, periodontists, general dentists or dental hygienists will administer the local periodontal therapy and re-treatment procedures as legally allowable under the locally applicable Dental Practice Acts governing the particular study site.

4.3. Periodontal Interventions

Periodontal intervention throughout the study includes:

- Scaling and Root Planing
- Extraction of Hopeless Teeth
- Local Chlorhexidine
- Oral Hygiene Instructions
- Supportive Periodontal Therapy

These procedures are described in detail below:

4.3.1. Scaling and Root Planing

Subjects randomized to the Treatment Group will receive full-mouth intensive periodontal care for removal of subgingival dental plaque biofilms with the use of scaling and root planing after the administration of local anesthesia (2% xylocaine with epinephrine 1:100,000 or alternative). The number of sessions will be based on the length of time needed to fully treat each patient. Emphasis will be on thorough scaling and root planing to achieve complete removal of calculus, plaque and diseased cementum, particularly at challenging sites such as furcation involvement.

Initial gross supragingival ultrasonic debridement and removal of heavy calculus will be done with the Cavitron using the Gross Debridement Instrument and ultrasonic power set at half of a turn on the

instrument front panel. After gross calculus removal is completed, the Cavitron tip may be changed to a Thin Line Tip to proceed subgingivally, to the bottom of all pockets in the selected quadrants. Debridement will be supplemented with instrumentation utilizing manual curettes as needed. The end point of debridement will be to remove dental plaque and calculus from enamel and root surfaces. After the treatment of one quadrant is completed, the operator proceeds to treat the opposing quadrant in the same manner described above.

Subjects randomized to the Control treatment will receive subgingival scaling and root planing at Baseline and at the study Visit 4 (12 months after Baseline).

4.3.1.1. Subgingival Scaling and Root Planing Procedure

1. Connect Cavitron instruments with an adequate water irrigation system.
2. Set up for visit with Cavitron with needed tips, instrument tray including manual dental curettes, a sterile sharpening stone, sterile 2x2 gauze, cotton rolls, etc.
3. Anesthetize the upper and lower quadrant on the same side from the distal of the last tooth to the midline. Use nerve blocks or regional anesthesia as appropriate, infiltration anesthesia when indicated. For the nerve blocks, regional and infiltration anesthesia use 2% Lidocaine with 1:100,000 epinephrine. In cases where excessive gingival inflammation is present, after block or infiltration anesthesia has taken effect, injection of interdental papilla with 2% Lidocaine with 1:100,000 epinephrine may be performed. If Lidocaine or epinephrine are contraindicated, use acceptable alternate drugs.
4. Initial Ultrasonic Debridement: Start on the distal of the most posterior tooth of the given quadrant and proceed around the buccal aspects to the midline with the Cavitron placing the Gross Debridement Instrument along the axis of the tooth. Remove all gross supragingival calculus and plaque deposits first, moving then the tip subgingivally as far as it can be inserted into the periodontal pocket. Change to Thin Line Universal Straight Tip if appropriate. Debride all sites subgingival until sulcus depth resistance is felt. Debride all surfaces carefully, as you debride make sure that root surfaces are free of all visible deposits. Irrigate approximately 1 to 2 minutes per tooth as you proceed around the buccal/facial. Repeat the ultrasonic debridement from the lingual aspect, again debriding one to two minutes per tooth. After all hard tissue debridement is completed with ultrasonic instruments, scalers and curettes will be used to achieve proper root planing. It is important to go to the depths of the pocket and completely 360 degrees around each tooth to remove all plaque and calculus in the lateral and apical projections of the pockets. It is also important to remove as much of the diseased cementum as possible into which bacteria and calculus have penetrated.
5. Use a standard subgingival explorer to check all surfaces for calculus, smoothness and hardness.
6. Final Ultrasonic Debridement
    a. Debride again with the Cavitron under continuous water irrigation, approximately 30 seconds per tooth, from the buccal and the lingual as in the initial debridement. Concentrate on those areas that feel rough upon root surface testing. The total

ultrasonic debridement (initial and final) per 2 quadrants may use 500-1,000 ml of water.

b. If the interdental papillae become detached as a result of the hand curette instrumentation, sutures may be used on buccal and lingual papillae over the interproximal bone with single interproximal suture. Use 4.0 silk suture material, no dressing is to be used.

7. Chlorhexidine Irrigation

    a. Subjects randomized to Treatment Group will receive application of Chlorhexidine as a preprocedural rinse and as part of the subgingival scaling and root planing treatment. Upon completion of SRP all sites will be irrigated with CHX rinse using a syringe.

    b. Patients randomized to the Control Treatment Group will receive application of Chlorhexidine, as preprocedural rinse and locally at Visit 4 (15 months), following completion of periodontal treatment. Upon completion of SRP all sites will be irrigated with CHX rinse using a syringe.

4.3.2. Extraction of Hopeless Teeth

Hopeless teeth, i.e. class III furcation and/or grade 3+ mobility and/or periodontal lesions approaching within 3 mm of the apices, will be extracted as part of the therapy prior to Baseline visit.

4.3.3. Oral Hygiene Instructions

It has been established that plaque control instruction results in significant improvement of oral hygiene as evaluated from reduction of both dental plaque and gingivitis scores. Instruction in oral hygiene will include individual demonstration of Bass technique utilizing the hum toothbrush. Use of MW will be demonstrated. Interdental oral hygiene will include the use of interproximal cleaning aids such as dental floss (hello and Meridol superfloss), and interproximal brushes to be dipped into MW. Both written and oral instructions will be provided.

4.4. Safety Issues During Treatment Visit

4.4.1. Guidelines for Management of Elevated Blood Pressures During Therapy Visit

It is anticipated that patients in this study will, on occasion, present for therapy visits with elevated blood pressure. Local therapy and local anesthetic will not be administered when systolic blood pressure exceeds 160 mm Hg or when diastolic exceeds 100. The protocol is as follows:

1. Pretreatment BP measurement; initiate treatment if BP<160/100
2. Repeat measurement if BP >160/100
3. Allow subject to sit quietly for 3 to 8 minutes and repeat the measurement

4. If 2 out of 3 readings are < 160/100, initiate treatment and repeat measurement in 15-20 minutes during therapy visit
5. If 3 elevated readings, reschedule therapy visit.

4.4.2. Guidelines for Management of Patients Receiving Anticoagulant Therapy

For patients receiving treatment with anticoagulants, special precautions will be taken in order to avoid excessive bleeding and to minimize undue risk to the patient.

Discontinuation of oral anticoagulation may not be relevant in the vast majority of the patients. Under the unusual circumstance that study patients will be diagnosed to have new atrial fibrillation or other scenarios requiring oral anticoagulation. Current American Dental Association (ADA) guidelines advocate against discontinuation of oral anticoagulation for dental procedures including tooth extraction and scaling & root planing. https://www.ada.org/en/member-center/oral-health-topics/oral-anticoagulant-and-antiplatelet-medications-and-dental-procedures

We propose to use topical measures to reduce bleeding risk, including lessening of tissue inflammation and irritation (oral hygiene, tartar removal, chlorhexidine rinses) before extraction, a careful surgical technique with thorough socket curettage to remove the inflammatory and granulation tissue, followed by wound compression, suturing and compression with dressings impregnated with tranexamic acid or epsilon-aminocaproic acid, placement of fibrin adhesives, oxidized cellulose and gelatin sponges in the tooth socket has also been suggested, to help clot formation before suturing. The methods are preferable to discontinuation of anticoagulation or reversal which may increase cardiovascular events.

5. BEHAVIORAL COMPONENT

5.1. Introduction

Treatment Group subjects will receive behavioral intervention at T0-T4. Behavioral intervention encompasses a wide range of behavior change techniques (BCTs) and will depend on the type of visit. For in-person visits, dental professionals will deliver the intervention and provide scripted (standardized) advice, while for at-home (distanced) visits, the intervention will be delivered using text messages. The delivery of the intervention will be multifaceted to reflect previous learnings, which demonstrated a combination of face-to-face and distanced approaches to be more effective.

5.2. Face-to-Face delivery

Face-to-Face is the main vehicle for eliciting change, due to the greater impact of personal interaction and the greater weight placed on "being told" something in person rather than from a text message. During the face-to-face interactions, dental professionals will provide scripted/ standardised advice to the study participants.

During face-to-face delivery, it is important to consider the interplay between clinical evaluations by the dental professional and personal (patient) perceptions. Ideally, both should align, i.e., when the clinician sees clinical improvement, the patient should also feel more optimistic. However, in reality, it is likely that discrepancies between clinicians and patients will arise. Sometimes, patients might feel optimistic and confident about their oral health while the actual clinical status of the patient does not support that perception. With this particular project, and during face-to-face interactions, there is the likelihood of a range of combinations in the interplay between clinical evaluations and patient perceptions. For the behavioral intervention delivered face-to-face, the focus needs to be directed towards the following areas:

- Negative clinical evaluations will be targeted, irrespective of how the patient is feeling about their progress, as the patient's clinical status (oral hygiene level and disease status) is of key importance (see interplay between negative clinical evaluation x positive patient perception)
- Negative patient perceptions will also need to be specifically targeted since they can easily demoralize and demotivate patients, irrespective of their clinical status, from adhering to their oral health regime and from maintaining progress during the study.
- Positive and neutral patient perceptions will need to be both supported and recognised, since neutral perceptions are better than negative and can be easily turned into positive perceptions, which can act as a crucial lever for sustained change.

Detailed examples of applied behavioral advice will be provided on a separate guide that will also be used as part of the dental professional's training on delivering the behavioral component.

It is important to note that for the Face-to-Face approach, dental professionals will need to:

- Deliver information in a manner that participants fully understand using clear language without many technical terms, abbreviations and unnecessary details
- Personalize the general standardized information and advice so that is relevant for participants and (1) utilizes the personalized data collected by the connected toothbrush platform employed in this study and (2) employs the coaching capabilities of this platform
- Set SMART (Specific, Measurable, Achievable, Relevant and Timely) goals with participants to minimize risk of failure and maximize benefits of achieving a goal

This is particularly important for the first two in-person visits (baseline (T0) and T1) since at the beginning of the process there is the likelihood of more impact for the intervention. Also, at the beginning of the process, participants will be more open to changes than later on. In T2-T3, we will switch our focus on

those who are still struggling (perception) and have negative clinical evaluations whilst maintaining support for those doing well and those who show improvement (positive/average). Finally, for T4, we will provide a reminder of the achievements and the journey that each participant took so participants can remind themselves of their achievements and feel motivated to carry on with their improved regime at the end of the study.

5.3. Text messages

Text messages will be used as a complementary element to the face-to-face approach, playing a vital role in the creation and sustenance of participants' habits as well as acting as a reminder for what participants need to do at home to maintain good oral hygiene practices. Habits are formed by repeating a specific behavior overtime and text messages allow for frequent reminders and support of this process. Text messages will be personalized using participants' first names and follow a more intense to less pattern, where in the first weeks and months of the study, participants receive more text messages. In the pages that follow, an overview of the content of the face-to-face and the text messages approaches are presented. Each approach has tailored content and mechanisms of delivery depending on the timings of the overall study starting from T0 and ending after T4.

Summary of text messages' frequency

For all intervals starting from T0 ending after T4											
M1				M2				M3			
W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4
One day this week (day / evening)	One day this week (day / evening)	One day this week (day / evening)	One day this week (day / evening)	Once in this interval (day / evening)							Before in person visit

6. SPECIMEN COLLECTION

6.1. Specimen Collection Overview

Biological Specimens, including blood, gingival crevicular fluid, dental plaque, tongue biofilm, and saliva, will be collected at the Baseline (T0) and at every 3 month follow-up visit (T1-T4) until the final

visit at (T5). A blood sample (finger prick) will also be collected at the Screening Visit (S0). An oral rinse will be collected at the IMT/FMD visits and aMMP8 analysis performed chairside. Blood samples will be collected for biomarker analysis which will include serum C-reactive protein (CRP), fasting lipid profile, and hemoglobin A1C. Measurement of plasma proteins may also be conducted by LC-MS. Subgingival dental plaque samples will be collected for -omics analysis. Omics analysis of tongue biofilm may also be completed. Saliva and Gingival Crevicular Fluid will be collected for inflammatory biomarker analysis. Samples will be collected and processed at each enrollment center.

Biospecimen	**Volume**	**Timepoints**
Whole Blood	Approximately 40 ml *One drop from finger prick for A1c	S0*, T0, T1, T2, T3, T4, T5
Gingival Crevicular Fluid (GCF)	n/a	T0, T1, T2, T3, T4, T5
Dental Plaque	n/a	T0, T1, T2, T3, T4, T5
Tongue Biofilm	n/a	T0, T1, T2, T3, T4, T5
Saliva	Approximately 5mL	T0, T1, T2, T3, T4, T5
Stool (optional)	Approximately 500 mg	T0, T2, T4

6.2. General Description of Biospecimens

6.2.1. Blood samples

- 2 - 5 ml gold top tubes for serum (BD vacutainer; no additive; 2 per patient); aliquot contents into 2 ml vials.
- 4 - 6 mL lavender top tube for plasma and HbA1C (BD vacutainer with dipotassium EDTA; 1 tube per patient); aliquot contents into 0.5 mL vials
- 1 - 6mL tiger top tube for hs-CRP and lipids.

6.2.2. Gingival Crevicular Fluid (GCF)

Four samples will be collected from the deepest probing depth sites.

Samples will be collected onto filter paper strips (Pro Flow, Inc., Amityville, NY) at a constant period of time, and the volume will be determined using a Periotron 8000â. Samples will be wrapped in aluminum foil, sealed in a cryovial and placed into liquid nitrogen chair-side. Strips will be stored in liquid nitrogen (-80°C) until mediator analysis.

These GCF samples will be prepared for the determination of local levels of inflammatory biomarkers panel. GCF samples will be used to quantify specific protein levels within these samples by ELISA and/or using the FluorokineÒ MAP cytokine multiplex kits (R&D Systems, Inc. Minneapolis, MN) and LuminexÒ analyzer system (DeSoto, Texas).

For aMMP8 analysis, gingival fluid will be collected using paper collection strips and measurement will be made chairside using ORALyzer® EXPERT device following steps described by the manufacturer.

6.2.3. Remaining Oral and Stool Samples

- Subgingival dental plaque: 4 samples will be collected from the deepest sites (GCF sites matching)
- Tongue biofilm
- Saliva (5ml; unstimulated)
- Stool (optional): Prelabeled kits containing stabilizer solution, disposable gloves, plastic scoop in cap and shipping materials will be provided to the participants. Participants are asked to scoop a single sample from a bowel movement in the morning and complete a brief questionnaire about bowel habits and current collection circumstances. The sample will be enclosed in the shipping container per instructions and delivered in person or by FedEx shipment to the UNC sites where it will be stored at -80°C until analysis.

7. CASE REPORT FORMS (CRFs) AND SOURCE DOCUMENTATION

Source data are all the information in original records and certified copies of original records of clinical findings, observations, laboratory reports, data sheets provided by the sponsor or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records. In this clinical trial, visit forms, confirmation of enrollment, randomization, study group assignment, log of product dispensing, data from soft tissue and hard tissue examinations, data from periodontal examinations, and administration of Questionnaires (with the exception of the diet questionnaire) will be captured on electronic case report forms (eCRFs). Direct data entry into eCRFs will be captured and stored in the **UNC Dental Toolkit** or other high-quality technology platforms. Paper case report forms (paper CRFs) may be used to capture certain data, as well. Technology will produce secure and compliant audit trails in accordance with the FDA 21 CFR Part 11 Electronic Records, Electronic Signatures, and Eudralex Annex11: Computerized Systems regulations.

SPONSOR'S AND INVESTIGATOR'S OBLIGATIONS CONFIDENTIALITY

Confidentiality

All records of subject participation in this study are confidential and these records are available only to the investigator, specifically trained site personnel, supervising dentist/examiner, potentially the sponsoring company, Ethics/Institutional Review Board (IRB), Local Regulatory Agency and possibly the Food and Drug Administration of the United States (FDA). In addition, the identity of participating subjects must be protected.

Only investigators (and specifically trained clinical site staff) will collect and have access to a subject's private information (e.g., name, medical records, etc.). Investigators will assign a study number to subjects which will be used to conceal their identity on all case report forms and other documents prior to their sharing with the broader study team, including the sponsor. Documents that identify the subject by name (e.g., the signed informed consent form or health questionnaire) will not be transferred or submitted to the sponsor, and will be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate national or local authorities or to sponsor personnel to verify subject, product safety and study compliance. The results of the study may be published in a scientific journal or a government public clinical database. If any publication occurs, only the subject's study number/ID, gender and/or age may be used.

Data collection in the case report form

All study data will be recorded in the case report form, which may be electronic or paper. For paper case record forms, all entries will be written clearly in black ink. Only the principal investigator, sub-investigators, or study coordinators may make entries in the case report forms. If erroneous data are entered on the case report forms, corrections to the data must be made by crossing out the incorrect entry with a single line (such that the initial entry remains legible) and entering the correction. All corrections on a case report form will be initiated and dated by the investigator, sub-investigator, or study coordinator making the correction.

Documentation of Consent, privacy notice and storage of study documents

All informed consent forms will be documented in a log by date and subject ID; the log will be kept as source documentation. In cases where Informed consent forms may be signed on paper due to any technical issues, the informed consents will be stored in a secure locked room designated for research charts storage in the clinical site. The Investigator will provide each subject with a clear and understandable privacy notice regarding the processing in connection with the study of personal data (i.e., any information relating to an identified or identifiable individual) by the investigator, sponsor and other persons involved in the study. Each subject will be given a copy of the privacy notice and the privacy notice will be referenced in and form a part of the overall study-informed consent/notice process.

A baseline privacy notice is included in this protocol for that purpose. Any deviation to the privacy notice as regards processing by the sponsor (including its vendors, monitors and other representatives) must be agreed with by the sponsor. In addition, the Investigator is responsible for ensuring that the privacy notice includes any local requirements regarding data security and privacy laws and regulations applicable to the study and the subjects. Should the privacy notice fail to meet any applicable local requirements, the

Investigator is responsible for amending the privacy notice to bring it into compliance with local applicable regulations and the Investigator (including Principal and sub-Investigators) agrees to indemnify and be liable to the Sponsor for any damages resulting from such non-compliance.

Subjects' study charts will be stored in a secure locked room designated for research charts storage in the clinical site. The chart room is a limited-access area and only delegated study personnel will have access to the study charts and subjects' data.

Publication

All manuscripts or presentations based upon this study, including press statements and internal public notices and memoranda, must be submitted to the Sponsor for review and approval prior to release for publication or presentation. This review period will be up to 60 days in duration. Review of an abstract may be expedited in some circumstances.

Consent

Informed consent procedures and documentation for the Baseline Oral Health Study will comply with 45 CFR Part 46 and 21 CFR Part 50. Signed consent and HIPAA authorization will be obtained from each subject in the Baseline Oral Health Study.

Study personnel will be responsible for ensuring that valid consent is obtained and fully documented appropriately for all Baseline Oral Health Health Study subjects prior to performing any study-specific procedures. For subjects signing a hard copy ICF, the original signed and dated ICF will be maintained in a secure file at the clinical site and a copy of the ICF will be provided to the subject. The subject will be given adequate time to review the ICF and discuss any questions with the Investigator or his/her delegate.

Protected Health Information

In connection with the Study, Investigators or their delegates may collect “Protected Health Information” as defined in the HIPAA at 45 CFR 160.103 or other medical information that is subject to applicable state laws (collectively, “Health Information”). Investigators or their delegates will obtain a valid, enforceable and signed HIPAA authorization from subjects to allow Investigators or their delegates the permission to disclose the Study Data to the Sponsor and its delegate to use and disclose the Study Data as described in the Protocol. Each signed HIPAA authorization will be in a form approved by the Sponsor. It will comply with the requirements of HIPAA and other applicable laws and will be retained by the Investigators or their delegates for inspection by the Sponsor upon reasonable request. In the event the Investigators or their delegates discloses Health Information to the Sponsor, the Investigator or his/her delegate agrees to de-identify, in accordance with those standards set forth in 45 CFR 164.514 and/or code in accordance with Sponsor’s written instructions or the Protocol, any study data that the institution provides to Verily or to a third party designated by Verily.

Institutional Review Board (IRB)

The Baseline Oral Health Health Study will not begin without documented approval by an IRB. Over the course of the study, the Baseline Team will ensure:

- Protocol, ICFs and consents are reviewed and approved by the IRB prior to study initiation
- The IRB has reviewed and approved the nonsignificant risk designation for the devices where applicable that will be used in the study prior to deployment of the devices
- All existing amendments to the protocol and ICFs are be reviewed and approved by the IRB prior to implementation, except where necessary to eliminate apparent immediate hazards to subjects
- The Investigator or his/her delegate will maintain copies of communications from the IRB indicating approval of the protocol and ICFs and any amendments
- The Sponsor will be responsible for obtaining annual IRB renewal for the duration of the study

General Considerations

Sites participating in the study will be eligible to begin enrollment and eligible to receive study sensor technology (including devices) as described in this protocol, when the following has been received:

- Curriculum Vitae (CV) of the Investigator
- A signed Investigator agreement
- IRB approval
- IRB-approved consent form

In addition to the usual considerations of consent that apply to all studies, the four principal ethical considerations that guide operations are:

- Privacy: It is necessary to minimize the possibility that an unauthorized person will be able to identify the research subject associated with a particular sample, and to link "-omic" and clinical information in a way that violates that research subject's privacy.
- Disclosure: The Project Baseline Health Study database must have rules for deciding whether and under what circumstances the results of analyses will be disclosed to a research subject, a researcher, a clinician, or the subject's family.
- Protection from harm: The research subject must be protected from harm resulting from effects on insurability or other adverse discrimination, and psychological harms or family disruption.
- Commercial potential: The possibility that there may be commercial value must be explicitly considered.

Privacy

General Considerations

There are a number of general operating principles to safeguard research subjects' privacy. Below is a list of physical and operational security control measures that will be employed to protect subject data:

- Control and document the movement of equipment associated with information systems
- Guard the physical facilities against unauthorized entry and/or tampering
- Maintain records of repairs and modifications to the facilities and equipment associated with information systems
- Restrict entry to essential personnel only
- Provide for a sign-in and escorts in the facility when appropriate
- Restrict testing, revisions, and modifications to authorized personnel
- Provide for the restoration of the data and software in the case of a natural or man-made disaster
- Continue business and clinical operations in the aftermath of a disaster

Policies Around Access to Data

Below is a list of policies and minimum requirements around access to data:

- Each user must have an authenticated and approved reason for obtaining access to those resources
- An individual account is issued to an individual and is not to be shared with any other individual or group
- A shared password is considered to be a compromised password and must be changed immediately
- Every workstation must require the user to sign-on prior to accessing the workstation or network resources

8. PROTOCOL APPROVAL, STUDY MONITORING AND COMPLIANCE

Institutional Review Board

The clinical investigation, including the consent form, will be reviewed by an Institutional Review Board in accordance with Title 21 of the Code of Federal Regulations, Parts 50 and 56. Approval by the Board must be obtained prior to the initiation of the study.

The study will be conducted in compliance with Good Clinical Practice Regulations, the study protocol and protocol amendment(s). Designated personnel will audit this study to ensure protocol compliance. In addition, study data and the Final Report will be examined for completeness, accuracy and proper documentation.

Informed Consent and Other Written Information for Subjects

The informed consent form and any other written information for subjects should meet local requirements of language and interpretation. One copy of the signed informed consent form and any other written information will be given to the subject or legal representative and the original will be retained by the investigator in the study files. The informed consent form and any other written information prepared by the investigator must be reviewed and approved by the sponsor and by the Institutional Review Board prior to their implementation. The informed consent form must include all required elements in accordance with GCP guidelines.

Protocol Compliance

The investigator is obligated to follow the provisions and requirements of the study protocol accordingly. Any changes to the protocol must be implemented only through formal written protocol amendments and only upon joint approval by the sponsor and investigator. All protocol amendments must be reviewed and approved prior to implementation by the institutional review board. If a protocol amendment requires changes to the informed consent form, the revised consent form must also be approved by the sponsor and the IRB.

Departures from eligibility requirements may be allowed on a case-by-case basis by the medical monitor or other authorized sponsor representative. Such departures must be medically and scientifically justified, must be pre-authorized, and must be documented in the case report form and tracked as official eligibility waivers.

Study Monitoring

The study will be monitored by members of the Oral Care Clinical Research Department of Colgate-Palmolive at periodic intervals during the course of the study to ensure that the study is being conducted according to Good Clinical Practice Guidelines.

General Procedures

The Sponsor's study monitor will review the progress of the study as frequently as is necessary to ensure adequate and accurate data collection. Monitoring activities may include:

- Periodic on-site visits
- Telephone or virtual communications with the site
- Ongoing review of case report forms, clinical records, and administrative documents

All records pertaining to the study will be made available to the study monitor during each site visit. Routine monitoring visits will be planned and confirmed in advance, as much as possible, to allow adequate time to assemble these records. Unplanned visits may occur as dictated by study necessities.

Important agreements and discussions between the Sponsor and investigator should be documented for the study file. Examples include eligibility criteria exceptions, agreements to deviate from protocol-defined procedures, notifications of subject withdrawal, etc.

Reports

The final report for the sponsor will summarize the method, statistical analyses, data and conclusion relative to the test product, the subject completing the study and summarize any adverse events and deviations. Source data will be retained by the study site. Copies of the transcribed data will be incorporated in the final report as data tables.

Record Retention and Access to Source Data/Documents

Source documents must be kept for at least five (5) years after terminating the study. The Investigator will maintain all study documentation for all subjects entered into the study in a secure area, ensuring the confidentiality of the information collected. Securing records includes placing written forms in locked file cabinets and/or sealed and labeled storage boxes in a locked room. Access will be denied to all persons with the exception of the Principal Investigator and his/her designees. In the event that clinical records cannot be securely kept by the clinical site for the agreed upon duration of time, the study sponsor will be notified before the destruction of any study records occurs. The study sponsor maintains the right to keep the clinical records for the agreed duration of time.

9. STUDY PRODUCT MANAGEMENT

Study Products

Study products will be supplied by the sponsor for this study. The study investigator will verify that the quantity of supplies, protocol number, and identification numbers match the information on the shipping invoice, and will store and account for the study supplies as described below.

Study Products Storage, Handling, and Accountability

The study products must be stored in a secure area with limited access, at room temperature. The investigator is directly responsible for the accountability of all used and unused study products. The investigator and all sub-investigators will make every effort to remain blinded as to the subject regimen. Records must be maintained to document the receipt and disposition of all study supplies provided to the investigator by the sponsor. The study monitor will review these records periodically during the course of the study. At the end of the study, or as directed by the monitor, the investigator must return all unused study products to the sponsor.

10. CONCOMITANT THERAPY

If a subject takes concomitant medications as a matter of necessity for the treatment of a medical condition, then such medication may be permitted for the duration of the study at the discretion of the investigator. However, it is the responsibility of the investigator to disqualify from entering the study any subject who, upon screening, is using medication or consumer products that might obscure the interpretation of study results. All medications currently used by the subject at enrollment, or any time through the end of the study, will be recorded on medical history and visit form. Subjects may receive medication to treat adverse events as deemed necessary by the investigator or the subject's physician.

11. ADVERSE EVENTS

A. DEFINITIONS:

Adverse Events (AEs) and Serious Adverse Events (SAEs) are defined by the ICH Guideline for Good Clinical Practice (ICH GCP) as follows:

> Adverse Event: Any untoward medical occurrence in a patient or clinical investigations subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include any clinically significant deterioration of a subject's medical status, after being enrolled in the study and signing an Informed Consent form. The AE may involve any organs or systems and can be represented by the new onset or the deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change from baseline, including frequency or pattern changes for a fluctuating condition (e.g., migraine), occurring after the first administration of study medication is an adverse event. All such occurrences must be recorded and reported accordingly, whether they appear causally related to the study medication, or not.

Serious Adverse Event: Any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life threatening adverse event
- Inpatient hospitalization, or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

B. IMPORTANT NOTES:

The concepts of Adverse Event / Experience (AE) and Serious Adverse Event / Experience (SAE) represent regulatory instruments used to evaluate and monitor the safety of clinical trial subjects. Therefore, these terms only apply in light of their regulatory definition. The term "serious", in a regulatory sense, does not necessarily mean "severe". All adverse events (serious and non-serious) reported during a study will be taken into account when analyzing the study data and establishing the safety profile of the investigational drug, and will be included in the final study report. The SAE concept is primarily used to identify, during the conduct of the trial, those adverse events that may require an expedited reporting procedure to regulatory authorities.

Death: The outcome of death requires that the AE that resulted in death be reported as an SAE. Death, in and of itself, is not an AE; it is only an outcome. The cause of death is the AE; therefore, the investigator should make every effort to obtain and document the cause of death for all subjects who die during the study. If, despite all efforts, the cause of death remains unknown, the AE it should be documented as "unspecified fatal event".

Life-threatening Adverse Event: Any adverse event that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).

Hospitalization: It should be noted that hospitalization, in and of itself, does not represent an SAE. It is the adverse event leading to the subject's hospitalization that becomes "serious" when it requires

inpatient care. Consequently, SAE should not be reported in case of pre-planned hospitalizations for pre-existing conditions that did not worsen during the study.

Disability: A substantial disruption of a person's ability to conduct normal life functions.

C. REPORT AND DOCUMENTATION OF ADVERSE EVENTS:

Expected Adverse Effects:

To blood draws

- Hematoma and/or soreness at the site of the puncture

To Periodontal Treatment:

- Tooth sensitivity
- Oral bleeding
- Gingival swelling
- Possibly minor bruising, bleeding or soreness at the anesthesia injection site during application

To X-Ray (Full Mouth) Series -S0 and T5:

- This research study involves exposure to radiation from two full mouth series (14 periapicals and 4 vertical bitewing projections per series). Please note that this radiation exposure is not necessary for medical care and is for research purposes only.
- For comparison, the average person in the United States receives a radiation exposure of 0.3 rem (or 300 mrem) per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth's air and soil.
- The dose that a subject will receive from participation in this research study is less than the amount received from these natural sources in one year.
- The amount of radiation the subjects will receive in this study has a minimal risk and is below the dose guideline established by The University of North Carolina Radiation Safety Committee for research subjects.

General Procedures for All Unexpected Adverse Events

All clinical complaints, symptoms, or signs that meet the adverse event definition, except expected adverse events listed above, will be recorded on the Non Serious Adverse Events case report form (CRF) using a recognized medical term or diagnosis that accurately reflects the event. Source documentation should be maintained that allows for clear identification of each adverse event and the following
parameters required for the CRF:

- AE description
- Date of onset
- Date of resolution
- Outcome

- Severity
- Seriousness
- Relationship to study drug (causality)
- Actions taken

Adverse events will be assessed by the investigator or designee for severity, relationship to the study product, possible etiologies, and whether the event meets the criteria as a serious adverse event and therefore requires immediate notification of the sponsor.

For CRF data collection purposes, the outcome of all adverse events recorded on the Adverse Event form should be reported within two (2) weeks of the study completion. The investigator will include this information in the Site Report providing a line listing using the Periodic/End of Study Report Form and attaching the individual adverse event form for each case reported. However, the investigator is responsible for following all adverse events until resolution or until no longer of clinical concern, and providing these data to the sponsor.

When protocol duration is six (6) months or longer, a Periodic/End of Study Report Form must be completed and included as part of your Site Report every six (6) months for the duration of the protocol.

Reporting Procedures for Serious Adverse Events

Any adverse event that is serious or potentially serious requires additional detailed reports and follow-up. A serious adverse event must be reported to the sponsor's representative immediately (within 24 hours of the investigator learning about the event). A Serious Adverse Event Report Forms must be completed so as to facilitate discussion and implementation of necessary follow-up measures, and to enable the sponsor to submit necessary reports to regulatory authorities and other investigators. Once the sponsor reviews the Serious Adverse Event Report Form, additional information may be requested from the investigator to allow appropriate medical evaluation and determine the regulatory reporting requirements.

The investigator is responsible for following all unexpected adverse events, especially those deemed "serious," until resolution or until the event is no longer of clinical concern, and for providing all data to the sponsor in an agreed-upon format. The investigator is also responsible for reporting all serious adverse events to the Institutional Review Board (IRB) overseeing the conduct of the study at the respective study center, according to the rules and procedures established by this committee.

12. SUBJECT TERMINATION/WITHDRAW PROCEDURES

A genuine effort will be made to determine the reason(s) why a subject fails to return for the necessary visit(s) or is dropped from the study. Subjects could be dropped from the study if any of the following occur:

1. Subject fails to substantially comply with the protocol requirements.
2. Subject fails to report for a scheduled examination.
3. Subject is treated with medication(s) during the course of the study, which may interfere with the parameters under study.
4. Subject receives emergency dental or medical treatment, which may interfere with the parameters under study.
5. Subject develops a serious adverse reaction. The Study Investigator will immediately notify the study monitor and information will be recorded on an Adverse Reaction Form.
6. Sponsor elects to terminate the study.
7. Subject elects to terminate participation in the study.

A study Visit Form indicating end of study participation must be completed for all subjects entered into the study even if they do not complete the study.

13. NEW FINDINGS

Subjects will be informed of any significant new findings related to study products or procedures when they become known during the course of this clinical research study. Such information may affect the subject's decision to continue participation in the study.

14. STATISTICAL ANALYSIS AND SAMPLE SIZE

14.1. Statistical Analysis

14.1.1. Descriptive Analyses

Descriptive summaries of baseline and longitudinal data will include the number of observations, mean, standard deviation (SD), median, and range for continuous variables. Categorical data will be summarized using the number of observations and percentages.

Descriptive analyses will be performed for the overall enrolled study population as well as for subgroups defined by comorbid disease category and assigned treatment group.

14.1.2. Primary Analyses

Analyses associated with the first primary outcome, the impact of treatment on oral health measures, will be performed using generalized estimating equations (GEE) methods. Longitudinal outcomes in the Treated vs. Control groups will be compared and will include all subjects who were randomized and their data from visits T1 - T4 based on intent-to-treat (ITT) group assignment.

The second primary outcome, association between changes in oral health and changes in systemic health, will be evaluated using correlation analysis. Changes in the measures of oral and systemic health between Baseline (T0) and follow-up visit 4 (T4) will be calculated for all subjects in the study who complete the T4 visit. The strength of correlations between changes in oral health and change in HbA_{1c} (in subjects with prediabetes or type 2 diabetes) or change in flow mediated dilation will be evaluated.

14.1.3. Secondary Analyses

All secondary outcomes will be evaluated using the ITT population and GEE methodology. Systemic outcomes that are only applicable to a particular comorbid disease subgroup will only be evaluated in that population. Specifically, flow-mediated dilation and Carotid intima media thickness (IMT) will be evaluated in all subjects.

14.1.4. Exploratory Analyses

Among those who meet all initial screening criteria and receive an oral health screening, we will analyze the prevalence and severity (Stage I, II, III) of periodontal disease, overall and by subgroups of interest (e.g., demographic characteristics, comorbidity disease category, etc.). Other details of exploratory analyses may be described in the Statistical Analysis Plan.

14.2. Sample Size and Power

This study is powered to detect a mean reduction in periodontal probing depth of 0.88 (SD 0.5) mm over the course of 12 months of periodontal therapy in the Treated group, versus a mean reduction of 0.63 (SD 0.59) mm in the Control group. Assuming a 2-tailed test with $\alpha = 0.05$, we need 200 subjects (100 per group) to have 90% power to achieve statistical significance. Assuming a 10% drop out during the study, this means we need to recruit approximately 200 - 224 subjects (112 per Control and Treatment group). If the dropout rate is found to be greater than 10%, additional recruitment may be required to achieve the target of approximately 100 - 112 per group.

For the correlation analyses, we can assume various distributions of prediabetes, type 2 diabetes, and cardiovascular disease among the study cohort (note that subjects may qualify for more than one category). Given the total sample size of 224, the table below describes the effect sizes (i.e., Pearson correlation coefficients) this study would have the power to detect with various cohort distributions and power levels.

Correlations able to be detected in a subgroup, by sample size and power

	Cohort representation, out of overall study population, N = 224			
Power	1/6, N = 37	1/4, N = 56	1/3, N = 75	1/2, N = 112
70%	0.422	0.346	0.300	0.247
80%	0.468	0.386	0.336	0.277
90%	0.528	0.439	0.384	0.317

Note: $\alpha = 0.0$

15. APPENDIX

PRIVACY NOTICE

This privacy notice describes how information relating to you (i.e., personal data) is collected and used in relation to the study for which you have completed an Informed Consent Form. In particular, it describes the safeguards in place to protect your personal data from disclosure, and your rights with respect to them. Please take a moment to familiarize yourself with its content, ask any questions you may have, and complete it where appropriate.

INTRODUCTION

When you join the study, specifically trained individuals, in particular those known as investigators, such as your dentist or a research scientist, will act as your primary point of contact and collect personal data about you. Prior to disclosing such personal data to the larger study team, including Colgate Company, sponsoring the study, investigators and their team will code your personal data. The larger study team will therefore only obtain and access data about you in a coded format, except in limited circumstances described below. This Privacy Notice provides a general description of how investigators and their team collect/use your personal data (section 1), how the larger study team uses your coded data (section 2), how your data may be transferred and stored (section 3) and your rights in that regard (section 4).

This privacy notice also contains a section at the end for you to complete. Please make sure to do so.

SECTION 1 – USE OF PERSONAL DATA (NON-CODED AND CODED) BY THE PRIMARY STUDY TEAM

This Section specifically describes how the study staff with whom you may interact uses the personal data about you (regardless of whether it is coded or not).

What personal data will the primary study team collect and why?

If you join this study, investigators, their authorized support staff and other specifically trained individuals ("**Primary Study Team**") will collect and use your personal data as part of the study. The personal data could include your name, address, date of birth, other personal (e.g., language) and contact details, and data about your health and study results.

The personal data about you collected by the Primary Study Team may include:

- Weight, height, age, gender or other demographic and/or physical information.
- Use of tobacco products and dietary habits.
- Results from study tests, questionnaires and blood tests.
- Information contained in informed consent and case report forms.
- Sensitive data such as racial origin (e.g., through photographs), consumption habits or pregnancy status if necessary for the conduct of the study, for example to verify inclusion or exclusion criteria.
- Relevant above data sets as subsequently coded.

The personal data above will be collected directly from you, for example during exams, or as part of your medical history. Some personal data may also be collected from publicly available databases. Note that the provision and use of personal data under the study is required and that, absent such provision, you may not be able to participate in the study.

The Primary Study Team may collect and use your personal data for the following purposes:

- **Data collection and coding** – To add you to the study initially and to collect information during the conduct of the study including visits, exams, history review, coding the personal data and transmitting it to Colgate Company. The Primary Study Team may engage in this activity with your consent which you are requested to provide at the bottom of this form.
- **Scientific research**
    - To perform the research as described in the Informed Consent Form, including:
        - Assessing the effects of relevant products.
        - Combining data obtained with data from other sources and analyzing results.
        - Developing and commercializing new products, solutions and treatments.
        - To apply, or assist in applying, for authorizations regarding the products.
    - To publish results of research study in a study report or scientific presentation. Information that identifies you or that reasonably could be used to identify you publically, such as your full name, will not be included in such publications.
    - Further scientific research, such as retrospective or prospective studies and training and education in connection with the study and its outcome.

The Primary Study Team may engage in this activity for scientific research or health care or treatment.

- **Adverse events and reactions management and reporting, health threats, and health standards**

The Primary Study Team may use your personal data in the above activities to protect your vital interest, to address a serious cross-border threat to health, to ensure high standards of quality and safety of healthcare and medicinal products, or for scientific research.

- **Legal and regulatory compliance, study monitoring and request management**

The Primary Study Team may use your personal data in the above activity where required by a substantial public interest set out by law, to comply with mandatory requirements or legal authorizations, managing requests from individuals, regulatory oversight and requests, to verify and audit the study and ensure a high standard of privacy, quality and safety for the study and its subjects, for health care or treatment, or in case of the establishment, exercise or defense of a legal claim.

Who will have access to your personal data?

A distinction must be drawn between your personal data in a non-coded form and your personal data in a coded form. Only the Primary Study Team and a limited number of other persons listed below can have access to your personal data in a non-coded form, which may allow your direct identification (e.g., through

your name or other direct identifiers). Apart from that, as explained further in the next section, the Primary Study Team will replace information that directly identifies you such as your name, with a key code before disclosing such data to any other person. Only specific individuals will have the key to unlock the code. Also, your coded data will remain subject to strict access limitation and shared on a need to know basis only.

Who can access my personal data in a non-coded form - Only a limited number of persons are authorized to do so. Aside from the Primary Study Team, these are people who may need to see this information to ensure that the research study is being or has been conducted properly, in accordance with laws and ethical requirements, including:

- The ethics committees that review the study to ensure that it meets ethical standards, in particular the protection of subjects.
- Study auditors who may verify and audit the study (who may be external or appointed by the company sponsoring the study).
- Regulatory agencies, administrations and other authorities that control the study, public health and subject or product safety, and that oversee subsequent authorizations.
- Verily and the Foundation (Stanford University and Duke University).

Who can access my personal data in a coded form – Aside from the Primary Study Team and persons identified just above, only the larger study team and persons they choose to share the data with are authorized to access your personal data, in principle in a coded form only, as explained in the next section.

SECTION 2 – USE OF YOUR CODED DATA BY THE LARGER STUDY TEAM

- As explained above, the Primary Study Team will replace information that directly identifies you (e.g., your name or contact information) with a code, possibly along with your gender and age ("**Your Coded Data**"), before disclosing or reporting study data associated with those identifiers to the larger study team including members of Colgate Company, sponsoring the study (the "**Larger Study Team**"). This Section describes the permitted uses of Your Coded Data.

How will Your Coded Data be used?
The Larger Study Team may use Your Coded Data for the following purposes:
Data collection – To collect Coded Data from the Primary Study Team, and use the Coded Data as part of your active participation in the study.
The Larger Study Team may engage in this activity with your consent as requested at the bottom of this form.

- **Scientific Research** – To perform the research as described in the Informed Consent Form, including:
    - To evaluate the results of this study and research.
    - Developing and commercializing new products, solutions and treatments.
    - To apply for authorizations regarding products.

- To learn more about products and how they work on the body.
- To help with the design of future studies.

The Larger Study Team may engage in this activity for scientific research or health care or treatment.

- **Further studies** – For future scientific research projects, the specific details of which may not be known at present, to advance science and public health. The Larger Study Team may engage in this activity for scientific research or health care or treatment.
- **Adverse events or reactions, health threats, and health standards --**

The Larger Study Team may use Your Coded Data to protect your vital interest, to address a serious cross-border threat to health, to ensure high standards of quality and safety of healthcare and medical products, or health care or treatment.

- **Legal and regulatory compliance, study monitoring and request management**

The Larger Study Team may use Your Coded Data where required by a substantial public interest set out by law, to comply with mandatory requirements or legal authorizations, managing requests from individuals, regulatory oversight and requests, to verify and audit the study and ensure a high standard of privacy, quality and safety for the study and its subjects, for health care or treatment, or in case of the establishment, exercise or defense of a legal claim.

Who will have access to your Coded Data?

The Larger Study Team – Within the Larger Study Team, only specific and trained individuals may generally have access to Your Coded Data, such as statisticians and data managers or analysts.

Other persons - In addition, the Larger Study Team may disclose Your Coded Data to specific persons on a need to know basis, in particular:

- Providers of hosting services that store Your Coded Data, organizations that work with the Larger Study Team to facilitate the study, or professional advisors to help exercise legal rights.
- People who may need to see Your Coded Data to ensure that the research study is being or has been conducted properly, in accordance with laws and ethical requirements, including:
    - The ethics committees that review the study to ensure that it meets ethical standards, in particular the protection of subjects.
    - Study auditors who may verify and audit the study.
    - Regulatory agencies, administrations, scientific boards and other authorities that control the study, public health and subject or product safety, and that oversee subsequent authorizations.
- Further to mandatory public disclosure requirements, such as the publication of age and gender on global clinical websites.

SECTION 3 - HOW WILL YOUR DATA BE TRANSFERRED AND STORED?

Your personal data and Coded Data may be sent to countries around the world where the study and its follow-up is taking place or operated from, or where Colgate Company seeks to market its products,

including outside your country of residence. The data protection laws in these countries may be different from the data protection laws in the country in which you are participating in the study.

The Primary Study Team and the Larger Study Team will retain personal data and Your Coded Data respectively for as long as needed or permitted in light of the purpose(s) for which they were obtained and consistent with applicable law. The criteria used to determine such retention periods may include:

- Whether there is a legal or regulatory obligation to which the Primary Study Team or the Larger Study Team are subject (for example, certain laws require to archive certain data or files for several years after the end of a study).
- Whether retention is advisable in light of the Primary Study Team or Larger Study Team's legal position (such as in regard to applicable statutes of limitations, litigation or regulatory demands).
- Technical and operational standards, such as ensuring system and data integrity, continuity availability and resilience, including preventing study or data biases or corruption.

SECTION 4 – YOUR RIGHTS

This Section explains your rights as regards your personal data.

You have the right to request to review, correct, delete, restrict, object to the use or receive a portable copy of your personal data. Note that such rights may be suspended or restricted under the study, or that exercising them may affect your participation in the study. For example, if you obtain access to your study records during a study where you are not supposed to know whether you are receiving actual medication or a placebo, you may not be able to continue participating in the study. Similarly, there may be legal or regulatory requirements to retain data that have been collected as a part of a study, despite your right to request their deletion. Moreover, if Your Coded Data has been used in a publication, it may not be possible to delete it.

To submit a request regarding your personal data, please contact your study investigator. For more information about your privacy rights, or if you are not able to resolve a problem directly with us and wish to make a complaint, you can contact a data protection authority in the EEA State where you have your habitual residence, place of work or where an alleged infringement of EEA data protection rules may have occurred.

Consent

What happens if I change my mind?

Even after you consent, you have the right to withdraw your consent at any time. Should you choose to withdraw your consent, your investigator (or another member of the Primary Study Team) may ask you to undergo an end of study examination, and will thereafter stop collecting your personal data as part of this study. You should know that if you withdraw your consent, you will not be able to continue taking part in the study. Further, you should understand that data that has already been collected may not be able to be deleted from study records due to regulatory requirements that are designed to safeguard scientific integrity. The Primary Study Team and the Larger Study Team may be required to include your personal data in analyses and aggregated study results, but you will not be personally identifiable by name in such reports.

Also, contact information or emergency contact details which you provided, may be used by the Primary Study Team and other persons in order to re-establish contact with you, if necessary for subject safety reasons, reporting duties or a vital interest, such as a life status check. Publicly available information such as public registers or social media may be used for these purposes.

To withdraw your consent to the collection, use, and disclosure of your personal data, you may contact the study Principal Investigator.