University at Buffalo
The State University of New York
University at Buffalo Institutional Review Board (UBIRB)
Office of Research Compliance | Clinical and Translational Research Center Room 5018
875 Ellicott St. | Buffalo, NY 14203
UB Federalwide Assurance ID#: FWA00008824

# Complete Research Protocol (HRP-503)

## Table of Contents

## *Template Instructions*

***Sections that do not apply:***

- *In several sections, the addition of checkboxes for **Not Applicable** have been added to the template as responses.*
    - *If an N/A checkbox is present, select the appropriate justification from the list.*
    - *If an N/A checkbox is not present, or if none of the existing checkboxes apply to your study, you must write in your own justification.*
- *In addition:*
    - *For research where the only study procedures are records/chart review: Sections 19, 20, 22, 23, 24, 25, 31, and 32 do not apply.*
    - *For exempt research: Sections 31 and 32 do not apply.*

***Studies with multiple participant groups:***

- *If this study involves multiple participant groups (e.g. parents and children), provide information in applicable sections for each participant group. Clearly label responses when they differ. For example:*

  Response:

  Intervention Group:

  Control Group:

***Formatting:***

- *Do not remove template instructions or section headings when they do not apply to your study.*

*If you are pasting information from other documents using the "Merge Formatting" Paste option will maintain the formatting of the response boxes.*

***Amendments:***

- *When making modifications or revisions to this and other documents, use the **Track Changes** function in Microsoft Word.*
- *Update the version date or number **on Page 3.***

## PROTOCOL TITLE:

*Include the full protocol title.*

Response:

**Impact of Periodontal Therapy on Patients with Diabetes: A Pilot Study**

## PRINCIPAL INVESTIGATOR:

*Name*
*Department*
*Telephone Number*
*Email Address*

Response:

**Robert E. Schifferle, DDS, PhD**
**Oral Biology/Periodontics and Endodontics**
**716-829-2013**
**res@buffalo.edu**

## VERSION:

*Include the version date or number.*

Response: **3.1**

**March 02, 2022**

## GRANT APPLICABILITY:

*Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.*

*NOTE: This question does not apply to studies funded by a sponsor contract.*

*Include a copy of the grant proposal with your submission.*

Response: **Funding by Sunstar has ended; this is now an unfunded study.**

## RESEARCH REPOSITORY:

*Indicate where the research files will be kept, including when the study has been closed. The repository should include, at minimum, copies of IRB correspondence (approval, determination letters) as well as signed consent documents. This documentation should be maintained for 3 years after the study has been closed.*

Response: **Study documents will be kept in the Periodontal Disease Research Center (PDRC), Foster Hall, UB South Campus and include clinical records and Informed Consents.**

*Location:* **UB South Campus, PDRC, Foster Hall**

*Address:* **120 Foster Hall**

*Department:* **Oral Biology**

## 1.0 Objectives

*1.1 Describe the purpose, specific aims, or objectives of this research.*

Response: **Our main goal is to evaluate the efficacy of Supportive Periodontal Therapy (SPT), 0.12 % Chlorhexidine gluconate rinse (Paroex®) and Soft-Picks, after professional Scaling and Root Planing (SRP) on clinical, microbiological and immunological status in subjects with type 2 diabetes. Our second goal is to compare the response to periodontal therapy (SRP only versus SRP + SPT) in participants with and without diabetes. A clear understanding of how periodontal therapy affects clinical status and the microbiome could help to develop an effective treatment regimen for each subject.**

*1.2 State the hypotheses to be tested, if applicable.*

*NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.*

**Response:**

**1. Supportive Periodontal Therapy (SPT) using Paroex® mouthrinse (0.12% chlorhexidine) and Soft-Picks leads to improved clinical status and change in oral microbiome greater than when Scaling and Root Planing (SRP) only is used.**

**2. There will be about 35% who will be "Poor Responders" (PRs) (those needing Rescue Therapy). The number of PRs in diabetics will be higher than in non-diabetics. Poor Responders will have different clinical and microbiome in characteristics than responders.**

## 2.0 Scientific Endpoints

*2.1 Describe the scientific endpoint(s), the main result or occurrence under study.*

*NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should **not** be a date.*

1. *Response:* Primary endpoints;

**Primary Endpoints:**

**1. Change in Probing pocket depth (PPD) at the 6-month post-SRP completed at Baseline.**

**Secondary Endpoints:**

**1. Oral clinical variables: Changes in Bleeding on Probing (BOP), Clinical attachment level (CAL), and Gingival Index and Plaque Index (PI) at 3, 6, 9, and 12 months after treatment (Baseline); Change in PPD at 3, 9, and 12 months after treatment.**

**2. Systemic variables: Changes in Hemoglobin A1c (HbA1c); Fasting blood glucose (FBG); Immunoreactive insulin (IRI); High sensitivity C-reactive protein (hs-CRP); at 3, 6, and 12 months after treatment. Blood for C-peptide; proinsulin; total GLP-1, PYY, dipeptidyl peptidase-IV (DPP-IV); glucagon; plasma endotoxin (LPS); soluble TNF-α RI and RII; the dicarbonyl methylglyoxal (MGO), and Trimethylamine-N-Oxide (TMAO) will be collected at 3, 6, and 12 months study visits, but tested later.**

**3. Microbiology endpoints: Changes in Subgingival salivary and gut microbiome after periodontal treatment (SRP or SRP + SPT). Changes in the skin and vaginal microbiome after treatment will be assessed as resources permit.**

## 3.0 Background

*3.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.*

Response:

**Type 2 diabetes mellitus is a metabolic disease with high blood glucose levels due to either low or lacking insulin production or failure to properly respond to insulin. Diabetes affects more than 400 million people world-wide and the number is increasing each year. Continuously high blood glucose levels lead to many complications, for example, retinopathy, nephropathy, neuropathy, and cardiovascular disease. Complications of diabetes lead to significant morbidity and mortality as well as to a decrease in quality of life (QOL).**

**Diabetes and periodontal disease are also related and in a bidirectional manner. With poorly controlled blood glycemic levels,**

**periodontal status is often aggravated,[1,2] and severe periodontal conditions are associated with poorer glycemic control.[3] Systematic reviews and meta analyses conclude that periodontal disease leads to 0.36% to 0.65% reductions in hemoglobin A1c (HbA1c).[4,5] However, a multi-centered clinical trial showed non-surgical periodontal therapy did not improve glycemic control.[6] Borgnakke et al[7] reviewed the paper and found baseline HbA1c levels were already close to desired levels so there was little room for improvement. In addition, obesity could have influenced the results as it increases inflammation. A small percentage of patients even without diabetes do not respond well to SRP which could be related to poor home care, incomplete root planning and/or impaired or different host immune responses, or anatomic structures that preclude healing after therapy such as furcation clefts, enamel projections or other root abnormalities. Columbo et al[8,9] found distinctly different microbial profiles in those who did not respond well to periodontal therapy by using the Human Oral Microbe Identification Microarray in comparison to those who did.**

**In the past decade, the development of new next generation sequencing (NGS) techniques have shown a greater number of organisms that are related to periodontal disease than previously found when older assessment techniques were used. These older measures (for example, culturing) limited the number of bacteria that could be identified at one time and likely led to an incomplete understanding of the association between periodontal disease and diabetes. NGS allows for the characterization of hundreds of oral bacteria rather than a few leading to a more comprehensive assessment of the oral microbiome than was previously possible. The more complete assessment increases our ability to more fully examine the association between subjects with and without periodontal disease, those with and without diabetes and those with periodontal disease and diabetes versus those without either.[10,11] Genco et al[12] found correlations between periodontal status and the subgingival microbiome in diabetics; however, periodontal status has stronger correlations with subgingival microbiome composition than diabetes. In a pilot study, *Anaeroglobus* and *Parvimonas* are more abundant in subjects with diabetes and periodontits compared to those without diabetes but with periodontitis and those bacteria may be newly discovered periodontal pathogens.[12,13]**

**There are few published reports investigating the efficacy of periodontal therapy on the microbiome in diabetics. We hypothesize that the microbiome influences clinical response to periodontal therapy and systemic changes showing improvement in diabetes status, i.e., improvement in HbA1c. As an adjunct to the professional mechanical periodontal therapy, chlorhexidine gluconate rinse previously demonstrated significant clinical improvements especially the reduction of bleeding, gingival inflammation, and dental**

**plaque accumulation.[14-16] Moreover, interdental tooth cleaners removed more dental plaque effectively than only brushing and was followed by a reduction in gingival inflammation.[17] Therefore we developed the plan to add SRP or SRP + SPT to the non-diabetic groups to determine the differences in response between diabetics and non-diabetics. The main aim of this study is to evaluate the effects of Supportive Periodontal Therapy, 0.12 % Chlorhexidine gluconate rinse (Paroex®) and a rubber interdental bristle cleaner (Soft-Picks) after professional Scaling and Root Planning (SRP), on clinical, microbiological and immunological status of subjects with type 2 diabetes and periodontal disease. The second aim is to compare the response to Supportive Periodontal Therapy, SRP alone or SRP+SRP, between patients with and without type 2 diabetes. A clearer understanding of how periodontal therapy affects diabetes status could lead to the development of novel new targeted approaches to therapy of both periodontal disease and diabetes.**

*3.2 Include complete citations or references.*

Response:


**1. Nelson RG, Shlossman M, Budding LM, Pettitt DJ, Saad MF, Genco RJ, Knowler WC. Periodontal disease and NIDDM in Pima Indians. Diabetes Care. 1990 13(8):836-840.**

**2. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ. Non-insulin dependent diabetes mellitus and alveolar bone loss progression over 2 years. J Periodontol. 1998 69(1):76-83.**

**3. Arora N, Papapanou PN, Rosenbaum M, Jacobs DR Jr, Desvarieux M, Demmer RT. Periodontal infection, impaired fasting glucose and impaired glucose tolerance: results from the Continuous National Health and Nutrition Examination Survey 2009-2010. J Clin Periodontol. 2014 41(7):643-652.**

**4. Engebretson S, Kocher T. Evidence that periodontal treatment improves diabetes outcomes: a systematic review and meta-analysis. J Periodontol. 2013 84(4 Suppl):S153-69.**

**5. Sgolastra F, Severino M, Pietropaoli D, Gatto R, Monaco A. Effectiveness of periodontal treatment to improve metabolic control in patients with chronic periodontitis and type 2 diabetes: a meta-analysis of randomized clinical trials. J Periodontol. 2013 84(7):958-73.**

**6. Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W et al. The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. J Am Med Assoc. 2013 310:2523-2532.**

**7. Borgnakke WS, Chapple IL, Genco RJ, Armitage G, Bartold PM, D'Aiuto F, Eke PI, Giannobile WV, Kocher T, Kornman KS, Lang NP, Madianos PN, Murakami S, Nishimura F, Offenbacher S, Preshaw PM, Rahman AU, Sanz M, Slots J, Tonetti MS, Van Dyke TE. The multi-center randomized controlled trial (RCT) published by the journal of the American Medical Association (JAMA) on the effect of periodontal therapy on glycated hemoglobin (HbA1c) has fundamental problems. J Evid Based Dent Pract. 2014 14(3):127-132.**

**8. Colombo AP, Boches SK, Cotton SL, Goodson JM, Kent R, Haffajee AD, Socransky SS, Hasturk H, Van Dyke TE, Dewhirst F, Paster BJ. Comparisons of subgingival microbial profiles of refractory periodontitis, severe periodontitis, and periodontal health using the human oral microbe identification microarray. J Periodontol. 2009 80(9):1421-32.**

**9. Colombo AP, Bennet S, Cotton SL, Goodson JM, Kent R, Haffajee AD, Socransky SS, Hasturk H, Van Dyke TE, Dewhirst FE, Paster BJ. Impact of periodontal therapy on the subgingival microbiota of severe periodontitis: comparison between good responders and individuals with refractory periodontitis using the human oral microbe identification microarray. J Periodontol. 2012 83(10):1279-87.**

**10. Kirst ME, Li EC, Alfant B, Chi YY, Walker C, Magnusson I, Wang GP. Dysbiosis and alterations in predicted functions of the subgingival microbiome in chronic periodontitis. Appl Environ Microbiol. 2015 81(2):783-93.**

**11. Wang J, Qi J, Zhao H, He S, Zhang Y, Wei S, Zhao F. Metagenomic sequencing reveals microbiota and its functional potential associated with periodontal disease. Sci Rep. 2013 3:1843.**

**12. Genco RJ et al. The Subgingival `eriodontal Microbiome in Diabetes. The 3rd Microbiome R&D and Business Collaboration Forum 2015**

**13. Pérez-Chaparro PJ, Gonçalves C, Figueiredo LC, Faveri1 M, Lobão E, Tamashiro N, Duarte P, Feres M. Newly Identified Pathogens Associated with Periodontitis: A Systematic Review. J Dent Res. 2014 93(9):846-858.**

**14. Beiswanger BB, Mallat ME, Jackson RD, Mau MS, Farah CF, Bosma ML, Bollmer BW, Hancock EB. Clinical effects of a 0.12% chlorhexidine rinse as an adjunct to scaling and root planing. J Clin Dent. 1992 3(2):33-38.**

**15. Faveri M, Gursky LC, Feres M, Shibli JA, Salvador SL, de Figueiredo LC. Scaling and root planing and chlorhexidine mouthrinses in the treatment of chronic periodontitis: a randomized,**

**placebo-controlled clinical trial. J Clin Periodontol. 2006 33(11):819-828.**

**16. Abouassi T, Woelber JP, Holst K, Stampf S, Doerfer CE, Hellwig E, Ratka-Krüger P. Clinical efficacy and patients' acceptance of a rubber interdental bristle. A randomized controlled trial. Clin Oral Investig. 2014 18(7):1873-80.**

**17. Santos VR, Lima JA, Miranda TS, Gonçalves TE, Figueiredo LC, Faveri M, Duarte PM. Full-mouth disinfection as a therapeutic protocol for type-2 diabetic subjects with chronic periodontitis: twelve-month clinical outcomes: a randomized controlled clinical trial. J Clin Periodontol. 2013 40(2):155-62.**

## 4.0 Study Design

*4.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, observational).*

Response: **A single-center, single-blind, randomized controlled clinical trial:**

**Group A: Diabetic, Scaling & Root Planing (SRP) + Paroex® + Soft-Picks**

**Group B: Non-Diabetic, SRP + Paroex® + Soft-Picks**

**Group C: Diabetic, SRP**

**Group D: Non-Diabetic, SRP**

## 5.0 Local Number of Subjects

*5.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.*

Response: **104 with complete data; 26 per group**

*5.2 If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).*

Response: **250**

*5.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*

Response: **We have a list of participants in previous studies that have given us permission to re-contact them about new studies. We also have a successful history of being able to make and surpass recruitment goals. Tactics such as word of mouth, flyers and posters, and ads have worked well in the past.**

## 6.0 Inclusion and Exclusion Criteria

*6.1 Describe the criteria that define who will be **included** in your final study sample.*

*NOTE: This may be done in bullet point fashion.*

Response: **Inclusion Criteria: To be in this study subjects must meet all of the following criteria:**

**1) Be able to understand the informed consent form and be willing and able to read and sign it.**

**2) At least 25 years of age.**

**3) Be able to understand and follow directions for study procedures.**

**4) At least 14 natural teeth, not counting third molars ("wisdom teeth").**

**5) For moderate periodontal disease: At least four (4) teeth with at least one (1) site with ≥ 5 mm pocket depth (PD) and at least two (2) of the affected teeth with ≥ 2 mm alveolar bone loss as shown on radiographs. For Severe periodontal disease: At least eight (8) teeth with at least one (1) site with ≥ 5 mm pocket depth (PD) and at least two (2) of the affected teeth with ≥ 2 mm alveolar bone loss as shown on radiographs.**

*6.2 Describe the criteria that define who will be **excluded** from your final study sample.*

*NOTE: This may be done in bullet point fashion.*

Response: **Exclusion Criteria: Presence of the following criteria results in ineligibility for this study;**

**1) Presence of orthodontic appliances ("braces").**

**2) An abnormal condition of lips, lining of the mouth, tongue, or gums (except for periodontal disease). If subject has a cold sore, canker sore, or injury in their mouth, they may return after the sore or injury heals.**

**3) Abscess of the gingiva caused by periodontal disease, or visible gross tooth decay**

**4) A broken tooth root or an abscessed tooth, per clinician's judgement. Subject may be allowed to participate in the study after the condition is successfully treated or the study dentist reviews the condition and does not feel it will jeopardize the results of the study.**

**5) Periodontal treatment in the past 6 months.**

**6. Antibiotic therapy in the past three (3) months.**

**7) Have used cigarettes or other tobacco products in the past year.**

**8) Body mass index (BMI) is > 45.**

**9) Have regularly used non-steroidal anti-inflammatory drugs (such as >= 325 mg aspirin or ibuprofen) over the past 3 weeks.**

**10) Regularly using drugs that weaken the immune system (such as corticosteroids taken by mouth or injection, and cyclosporine).**

**11) Have participated in another clinical research study in the past 30 days.**

**12) Pregnant or breastfeeding.**

**13) Have a condition that we feel will make study participation unsafe or difficult for the patient.**

**14) Require premedication for dental exams.**

*6.3 Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.*

***NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.***

Response: **None.**

☐ Adults unable to consent

☐ Individuals who are not yet adults (infants, children, teenagers)

☐ Pregnant women

☐ Prisoners

*6.4 Indicate whether you will include non-English speaking individuals in your study.* ***Provide justification if you will exclude non-English speaking individuals.***

*In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may* ***not*** *be routinely excluded from research as a matter of convenience.*

*In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.*

Response: **We will not be actively recruiting non-English speaking subjects. This is a pilot study with the aim to obtain preliminary data that can be used for a larger proposal in the future. The expected number of subjects needed for this pilot does not warrant having the consent and surveys all officially translated into another language.**

## 7.0 Vulnerable Populations

*If the research involves special populations that are considered vulnerable,* ***describe the safeguards included to protect their rights and welfare.***

*NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.*

*7.1 For research that involves* ***pregnant women,*** *safeguards include:*
*NOTE CHECKLIST: Pregnant Women (HRP-412)*

Response:

☒ **N/A**: This research does not involve pregnant women.

*7.2 For research that involves* ***neonates of uncertain viability or non-viable neonates,*** *safeguards include:*
*NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)*

Response:

☒ **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

*7.3 For research that involves* ***prisoners****, safeguards include:*
*NOTE CHECKLIST: Prisoners (HRP-415)*

Response:

☒ **N/A:** This research does not involve prisoners.

*7.4 For research that involves* ***persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children")****, safeguards include:*
*NOTE CHECKLIST: Children (HRP-416)*

Response:

☒ **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

*7.5 For research that involves* ***cognitively impaired adults****, safeguards include:*

*NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)*

Response:

☒ **N/A:** This research does not involve cognitively impaired adults.

*7.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable.* ***Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.***

Response: **Students and employees may be screened and enrolled in the study if they meet eligibility criteria. However, their enrollment is not tied to student status or grades nor employee performance or evaluations.**

## 8.0 Eligibility Screening

*8.1 Describe* ***screening procedures*** *for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.*

📎 *Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaire)*

Response: **Potential participants may respond to flyers, posters, advertisements or word-of-mouth by phone call. First, they will be screened over the phone and if eligible, scheduled for a screening visit which may be the same day as the first study visit (Baseline Visit (if eligible)). A script will be used for the screening phone call plus a screening checklist. In the screening telephone conversation, women are asked if they are pregnant and are ineligible for the Screening Visit if they say yes. At the Screening visit, women of childbearing age are given a pregnancy test and if positive are ineligible. This testing is completed because of the possible need for Rescue Therapy if the study treatment is not successful. If the study treatment is not successful, the dentist/periodontist determines the nature and extent of the Rescue Therapy and it may include surgery and/or topical or systemic antibiotics. <u>The risk to any fetus from the study treatment is very low</u>. However, if topical or systemic antibiotics are required because of failure to respond to the study treatment, the risk to the fetus is higher. Hence, pregnancy tests will also be given at visits where additional therapy may be needed, and Arestin will <u>NOT</u> be given if the pregnancy test is positive.**In addition, AxiUm, the patient data system in the School of Dental Medicine, will be accessed to identify patients with diabetes who might be eligible, willing and interested in joining the study. For these patients, we will obtain permission of Dr. Joseph Gambacorta to contact identified patients, if he approves of the selection. Then an IRB-approved letter will be sent to the patients informing them of the study, telling then they may call us for more information or that we may call them to provide information about the study. Patients will also be told

they under no obligation to join the study. From there we will use the IRB-approved Telephone Screen Script and Screening Checklist to provide information to and assess eligibility of patient. All procedures thereafter will be the same as with other participants.

☐ **N/A:** There is no screening as part of this protocol.

## 9.0 Recruitment Methods

☐ **N/A:** This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections.

*9.1 Describe when, where, and how potential subjects will be recruited.*

*NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).*

Response: **Participants will be recruited from previous studies (if they have indicated they are interested participating in other/new studies), as well as from responses to posters, flyers, advertisements, and word-of-mouth. All advertising materials that will be used will be submitted to the IRB for approval <u>BEFORE</u> they are used. In addition, we plan to contact senior citizens' centers asking them to hang study posters and inform their participants about the study.**

**Radio and television ads will be used for recruitment when other methods have declining effect/no longer work and resources allow. Final versions of ads (radio and/or TV) will be submitted to the IRB for approval before use.**

**The AxiUm system, the patient data system in the School of Dental Medicine, will be accessed to identify patients with diabetes who might be eligible, willing and interested in joining the study. After receiving a partial HIPAA waiver for this work, we will request permission from Dr. Joseph Gambacorta to contact identified patients. If he approves, an IRB-approved letter will be sent to the patients informing them of the study, telling then they may call us for more information or that we may call them to provide information about the study. Patients will be told they under no obligation to join the study. We will use the IRB-approved Telephone Screen Script and Screening Checklist to provide information to and assess eligibility of patients. All procedures thereafter will be the same as with other participants.**

*9.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.*

*NOTE: Privacy refers to an individual's right to control access to him or herself.*

Response: **Potential and enrolled participants will interact with the study staff, the dentists, registered dental hygienists, dental assistants, laboratory technicians, research associates and data manager, in an operatory in the PDRC. If participants chose NOT to interact with one of these people, we can accommodate the request to a limited degree by having another dentist, hygienist, dental assistant or laboratory technician "work" with them, but once seen/examined by a dentist or hygienist we need to keep the same examiner for consistency of clinical examination data. Participants can ask to be seen in an operatory with a door that can be closed to better ensure privacy. Participants may also choose not to answer questions, but if those questions provide critical information needed to answer the research questions, the person will not be allowed to remain in the study. When participants have samples such as saliva collected, they are provided privacy from the view of others; blood is collected and height and weight measured out of the view of others as well.**

**The PDRC is a suite of rooms and operatories some of which have doors for privacy and quiet. However, even operatories without doors have limited access and view and so provide a good degree of privacy to everyone.**

**Participants "self-select" to join the study by calling us in response to flyers, posters and ads. They are told they may withdraw from the study at any time with no adverse effects on them. They are told we need certain data and that data need is explained prior to enrollment (at the time of the screening call and during the screening visit/first study visit.**

*9.3 Identify any materials that will be used to recruit subjects.*

*NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.*

*For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final audio/video tape. NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.*

Response: **Posters, flyers, ads and word-of-mouth, and AxiUm; a script is used for responses to these methods. All advertising materials that will be used will be submitted to the IRB for approval <u>BEFORE</u> they are used.**

## 10.0 Procedures Involved

*10.1 Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.*

*NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.*

Response: **SCREENING VISIT:**

**Subject will be recruited by advertisements, word-of-mouth, and by flyer and posters hung around the University and local community.**

**1. Consent: Visits will take place in the Periodontal Disease Research Center, 120 Foster Hall, UB South Campus. We will explain the study and study procedures to participants. If they agree to participate in the study, we will ask them to read and sign the consent form.**

**2. Demographic: Medical and dental histories and subject demographic information include date of birth, gender, racial and ethnic background, medical and dental histories, medications, lifestyle habits, dental home care, smoking status will be obtained. Height, weight, and blood pressure will be measured.**

**3. Oral health examination for eligibility: The oral health examination including measurements to assess teeth and gingival status will be completed. Dental radiographs will be taken unless suitable x-rays taken elsewhere within the past two years can be acquired. (Women of childbearing age will be required to take a pregnancy test before any radiographs are taken.)**

**4. Instruct in how to collect fecal samples at home, and give a fecal collection kit. Instruct to refrain from showering or washing hair for 24 hours before study visit.**

**5. Make an appointment for Baseline visit.**

**BASELINE VISIT:**

**1. Review medical and dental histories.**

**2. Baseline Taste Test**

**3. Oral Health Examination:**

**a) Plaque lndex (PI)**

**b) Probing Pocket Depth (PPD)**

**c) Bleeding on Probing (BOP)**

**d) Gingival Index (GI)**

**e) Clinical Attachment Level (CAL)**

**4. Collect samples:**

**a) Blood (FBS, HbA1c, Insulin, hs-CRP and microbiome testing, and for future testing of C-peptide, proinsulin, total GLP-1, PYY,**

**DPP-IV, glucagon, LPS, soluble-TNFα RI and RII, MGO, TMAO, creatinine, and for future unknown testing.**

**b) Subgingival plaque and saliva.**

**c) Fecal, skin, and vaginal samples**

**3. Treatment: All participants will receive full mouth SRP within one month of the baseline visit.**

**4. Oral health instruction: All participants will receive oral hygiene instruction from the hygienist.**

**5. Participants will be randomized into one of the four groups.**

**6. Groups A and B will receive the product, Soft-Picks, and information on how to use them.**

**7. Make an appointment for 3 months after Baseline Visit.**

**3-MONTH VISIT:**

**1. Collect the unused Soft-Picks and Paroex® bottle from the participants in the Groups A and B.**

**2. Ask the subjects to answer the Adverse Event, Taste and Compliance questionnaire.**

**3. Review medical and dental histories.**

**4. Taste Test.**

**5. Oral health examination**

**6. Collect saliva, subgingival plaque and stool/fecal samples.**

**6. Anterior teeth cleaning: All subjects will receive anterior teeth cleaning.**

**7. Groups A and B will have the product, Soft-Picks, replenished and usage instructions reviewed as needed.**

**8. Make or confirm the next appointment.**

**9. If any sites where pocket depths stay the same and are ≥ 5 mm or if the pockets deepen, periodontal treatment will be repeated. Exact treatment will be determined by the clinician (dentist or periodontist). The treatment will be explained to the participant and questions will be answered beforehand. Options for Rescue Therapy treatment are:**

- **Option 1: No additional treatment.**
- **Option 2: Pocket depths of ≥ 5 mm will receive scaling and root planing,**
- **Option 3: Pocket depths of ≥ 5 mm will receive scaling and root planing with the addition of a local antimicrobial agent,**

- **Option 4: Pocket depths of ≥ 5 mm will receive modified Widman flap surgery,**
- **Option 5: Pocket depths of ≥ 5 mm will receive modified Widman flap surgery with the addition of the GUIDOR® *easy-graft*® CLASSIC Alloplastic Bone Grafting System to infrabony defects that are amenable to regeneration.**

**6-MONTH VISIT:**

**1. Collect the unused Soft-Picks from the subjects in the Test Group.**

**2. Ask the subjects to answer the Adverse Event, Taste and Compliance questionnaire.**

**3. Review medical and dental histories.**

**4. Taste Test.**

**5. Oral health examination**

**6. Collect samples: blood (FBS, HbA1c, Insulin, hs-CRP and microbiome testing, and for future testing of C-peptide, proinsulin, total GLP-1, PYY, DPP-IV, glucagon, LPS, soluble-TNFα RI and RII, MGO, TMAO, creatinine, and for future unknown testing), subgingival plaque, saliva, fecal, skin, and vaginal samples.**

**7. Retreat all PD >= 5 mm sites. Subjects will receive additional treatment (Rescue Therapy), including surgery and/or topical or systemic antibiotics, if a clinician (dentist or periodontist) decides they need it. Rescue Therapy is standard of care for non-responsive periodontal lesions, the type depending on the clinical status of the participant. The need for Rescue Therapy (yes, no and type) will be noted in the study records and considered in the analysis of the study data. If on examination, a participant presents with an area showing a clinically defined worsening of their periodontal condition, rescue therapy will be initiated. This therapy will reduce the chance of the tooth being lost from periodontal disease. Rescue therapy will be provided to sites that remain at ≥ 5 mm or those demonstrating an increase in pocket depths of ≥ 2 mm from the baseline visit bringing them to or above the 5 mm level. Treatment will consist of scaling and root planing of the affected tooth and if the pocket depth is ≥ 5 mm, the site may also be treated by local drug delivery with Arestin. In women of childbearing potential, a urine pregnancy test will be provided prior to the placement of Arestin. If the pregnancy test is positive, Arestin will not be used in treatment. Local anesthetic may be used during the procedure as needed. Other treatments for saving the tooth may be given as deemed necessary by the dentist/periodontist clinician, as described above (Number 9 of the 3-**

**month Visit). The clinician will discuss the additional treatment with the participant before it is provided. The clinician providing the rescue therapy in a given subject should not be the clinician that will provide the periodontal measurements for that participant during the study.**

**8. Groups A and B will have the product, Soft-Picks, replenished and usage instructions reviewed as needed.**

**9. Confirm the next appointment.**

**9-MONTH VISIT:**

**1. Collect the unused Soft-Picks from the subjects in Groups A and B.**

**2. Ask the subjects to answer the Adverse Event, Taste and Compliance questionnaire.**

**3. Review medical and dental histories.**

**4. Taste Test.**

**5. Oral health examination**

**6. Retreat all PD >= 5 mm sites. Rescue therapy will be provided to sites that remain at ≥ 5 mm or to those demonstrating an increase in pocket depths of ≥ 2 mm from the baseline visit bringing them to or above the 5 mm level. Subjects will receive additional treatment (Rescue Therapy), including surgery and/or topical or systemic antibiotics, if a clinician (dentist or periodontist) decides they need it (as described in Number 9 of the 3-month Visit). Again, Rescue Therapy is standard of care for non-responsive periodontal lesions, the type depending on the clinical status of the participant. The need for Rescue Therapy (yes, no and type) will be noted in the study records and considered in the analysis of the study data.**

**7. Groups A and B will have the product, Soft-Picks, replenished and usage instructions reviewed as needed.**

**8. Make or confirm the next appointment.**

**12-MONTH VISIT:**

**1. Collect the unused Soft-Picks from the subjects in Groups A and B.**

**2. Review medical and dental histories.**

**3. Ask the subjects to answer the Adverse Event, and Compliance questionnaire.**

**4. Weight**

**5. Taste Test.**

**6. Oral health examination**

**7. Collect samples: blood (FBS, HbA1c, Insulin, hs-CRP and microbiome testing, and for future testing of C-peptide, proinsulin, total GLP-1, PYY, DPP-IV, glucagon, LPS, soluble-TNFα RI and RII, MGO, TMAO, creatinine, and for future unknown testing), subgingival plaque, saliva, fecal, skin, and vaginal samples.**

**8. Finish Study: Participants will receive a dental cleaning (prophy) and be referred to a dentist for any necessary dental treatment needed.**

*10.2 Describe what data will be collected.*

*NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.*

Response:

1. **Demographic information: age, date of birth, gender, racial and ethnic background**
2. **Medical History with Concomitant Medications**
3. **Dental History with Questionnaire to Assess Likelihood of Periodontal Disease**
4. **Height and Weight**
5. **Results of oral health examination and periodontal disease measurements**
6. **History of cigarette smoking and alcohol intake**
7. **Results of blood testing**
8. **Results of microbiome testing**

*10.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).*

*Include copies of these documents with your submission.*

Response:

**1. Medical History with Concomitant Medications**

**2. Dental History with Questionnaire to Assess Likelihood of Periodontal Disease**

**3. Forms – <u>uploaded to Click as file "DM RCT Manual of Procedures"</u>**

a. **Height and Weight Form**
b. **Blood Collection Form**
c. **Saliva Collection Form**

**d. Clinical Report Form for Charting Teeth Status and Periodontal Measurement Results**

**e. Plaque Collection Form**

**f. Fecal Collection Information Form**

**g. Vaginal Swab Collection Form**

**h. Taste Test Scoring Form**

**4. Study Visit Checklists for each visit**

*10.4 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).*

Response: AxiUm will be used to identify SDM patients with diabetes (see previous comments). **We will not use school records, medical records (electronic or otherwise), or other existing records; only those for the study. They are as follows:**

1. **Telephone Screening Checklist**
2. **Medical History with Concomitant Medications**
3. **Dental History with Questionnaire to Assess Likelihood of Periodontal Disease**
4. **AE, Taste and Compliance Assessment Questions Form**
5. **Blood Collection Form**
6. **Saliva Collection Form**
7. **Plaque Collection Form**
8. **Height and Weight Form**
9. **Fecal Collection Information Form**
10. **Skin Site Collection Form**
11. **Vaginal Swab Collection Form**
12. **Clinical Report Form for Charting Teeth Status and Periodontal Measurement Results**
13. **Study Visit Checklists including one for Rescue Therapy and Dental Prophy**
14. **Taste Test Scoring Form**

*10.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

Response: **The results of the blood tests for diabetes status will be shared with participants when received. The results of the dental examinations will be**

**shared with participants, and their dentists, or a dentist we refer them to, if they wish. The results of the testing if samples collected during the study will not be shared with participants. Testing will be completed after it could be of use to participants and it has not been determined how specific results affect individuals.**

*10.6 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.*

Response: **Study results will not be available until participants are finished with the study. If they ask about study results later, they will be given information on where to find publications or presentation. If this study is registered at ClinicalTrials.gov they will be told of this and given the study number.**

## 11.0 Study Timelines

*11.1 Describe the anticipated duration needed to enroll all study subjects.*

Response: **We estimate it will take 12-18 months to recruit and enroll 104 participants with complete data.**

*11.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.*

Response: **Each participant's duration of participation is approximately 12-13 months, slightly longer if study visits are not completed as scheduled.**

*11.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).*

Response: **Approximately 12-24 months.**

## 12.0 Setting

*12.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.*

*NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."*

Response: **The Periodontal Disease Research Center (PDRC), 120 Foster Hall, UB, 3435 Main Street, Buffalo, NY 14214. Research procedures will be performed in the operatories in the PDRC.**

**The Periodontal Disease Research Center at Buffalo was funded by the National Institutes of Health as one of their specialized clinical research centers for the study of periodontal disease. The center has been operational since 1977. The center comprises six operatories, an x-ray room, clean room for sterilizing instruments, an office, a waiting room and areas for support staff to have offices and places for meetings. Two of the operatories have doors allowing for additional privacy.**

**The PDRC's staff provides opportunities for dental and medical students, graduate students, and visiting scientists to participate in clinically oriented research projects. Since consistency of evaluations of periodontal status is necessary to limit measurement error in studies, the staff is regularly trained and calibrated in periodontal measurements. The staff also has provided training for many other examiners for other studies. As such, they are organized to provide this service.**

*12.2 For research conducted outside of UB and its affiliates, describe:*

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure*

*NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.*

Response:

☒ **N/A:** This study is not conducted outside of UB or its affiliates.

## 13.0 Community-Based Participatory Research

*13.1 Describe involvement of the community in the design and conduct of the research.*

*NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.*

Response:

☒ **N/A:** This study does not utilize CBPR.

*13.2 Describe the composition and involvement of a community advisory board.*

Response:

☒ **N/A:** This study does not have a community advisory board.

## 14.0 Resources and Qualifications

*14.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.*

*NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.*

Response: ***Principal Investigator: Robert E. Schifferle, DDS, PhD:*** **Dr. Schifferle is an Associate Professor in two departments in the UB School of Dental Medicine, Periodontics & Endodontics and Oral Biology. He is also Clinical Director of the Periodontal Disease Research Center; Clinical Group Director for Periodontics, and Director of the Pre-Doctoral Periodontics program for the 3rd and 4th year dental students. He is on editorial board of the NYS Dental Journal, and on the Peer Review Panel for the Journal of Periodontology. He is a consultant for ADA Council for Scientific Affairs, as well as being a periodontist with many years of clinical, laboratory, research and teaching experience. He has been an investigator and clinician for several clinical studies and has led or participated in calibration of examiners and treating of research study participants. He has been responsible for assuring that protocols were followed and data collected according to the protocol and MOP.**

**Dr. *Schifferle* has a long history of clinical and educational experiences and conduct of clinical and laboratory studies. His expertise in *clinical and theoretical* periodontal disease make him *well qualified to be Principal I*nvestigator of this study. He will *lead* analysis and interpretation of the data. He will also *lead and contribute to* the preparation of preliminary and final reports, manuscripts and presentations. He is eminently qualified to serve as the Principal Investigator of this study.**

***Patricia I. Diaz, DDS, MS, PhD, Investigator***: Dr. Diaz is Professor in the Department of Oral Biology, School of Dental Medicine and Director of the UB Microbiome Center. She is a periodontist and microbiologist with expertise in the study of the ecology and host interactions of the oral microbiome. As Investigator, Dr. Diaz will support this study and act as lead analyst of the data generated. She will be responsible for the overall analytic plan including preparation of preliminary and final reports, manuscripts and presentations.

***Karen L. Falkner, PhD, Project Coordinator:*** **Dr. Falkner is an epidemiologist with a background in nursing, education and research and has many years of experience with epidemiologic, cardiovascular and dental studies. In the past, she was Recruitment Coordinator for the Women's Health Initiative in Buffalo and regional recruitment chair for the Northeast area. She was project director of the study, Cognition in Long-term Recall of Physical Activity, and an international study of childhood leukemia in children exposed to fallout from the Chernobyl accident, conducted in Belarus, Ukraine and the Bryansk oblast in Russia. More recently, she has coordinated the BioCycle Study, the ExCel clinical trial for breast cancer prevention, and EAGeR (the Effects of Aspirin in Gestation and Reproduction), and several dental studies: the Biomarkers of Periodontal Disease Progression study, a study of the Effects of a Mouthwash Containing Chlorine Dioxide on Bacterial Plaque, the Periodontal Disease Screening Study, and the study, Screening of Patients in a Dental Setting for Diabetes Mellitus. Earlier studies were the Periodontal Infection and Risk for Myocardial Infarction study, the PAVE study, and the Sunstar Periocline and Wm. J. Wrigley Chewing Gum clinical trials. Dr. Falkner also has more than 10 years of experience coordinating studies where Dr. Genco is/was PI. Dr. Falkner has worked closely with multiple teams to organize and conduct dental training and calibrations sessions for dental examiners and training sessions for study protocol, for monitoring of study protocols, and to write and carry out procedures and policies for specimen collection, processing, storage and shipping.**
**Dr. Falkner will administer day-to-day activities of the study, and will oversee the logistical aspects of the project. She will monitor protocol, and assist in assuring that study activities and data collection are conducted in a timely and accurate manner. She will work with the other investigators and study staff at other centers for all aspects of the study. Dr. Falkner is well qualified to be study coordinator of this study.**

***Shannon H. Cervi, RDH, BA. Research Assistant:*** **Ms. Cervi will be responsible for patient recruitment, explaining and obtaining study**

**informed consent, administering study questionnaires, and providing ancillary support to the clinical staff preparatory to study evaluations, examinations, and treatments. She will provide administrative support with processing reports, scheduling appointments and will also be available to answer participant questions about the study. She has great skill and facility with the data systems and will work to ensure compliance with the study protocol. Ms. Cervi is or has been a study manager for several dental studies conducted at the Periodontal Disease Research Clinic. She has established relationships with many potential study participants which will assist with recruitment. She, with Mr. Dunford, will be responsible for the data entry of study questionnaires and other information. She is familiar with the conduct of clinical dental research, can take the oral radiographs for the study, and is well qualified to be a Research Assistant on this project. 03-29-2021: Since R. Dunford retired, Ms. Cervi will take on data management duties and give up many of her clinical duties. She will/has taken over all creation of data entry files, supervision of the process of double data entry with reconciliation of mismatches. Ms Cervi has been doing many data management tasks for several years and is well prepared to proceed as data manager.**

***Suzanne J. Andrusz, RDH, Dental Examiner:*** **Mrs. Andrusz will serve as one of the dental examiners/hygienist for the study. She has been trained and calibrated for many studies and is familiar with research study protocol and MOP rules and regulations. She can recruit and consent participants. Mrs. Andrusz is a dental hygienist with more than 30 years of experience. She is trained to do all parts of an oral health examination including radiographs, and can serve as an assistant and recorder if needed.**

***Yoshiko Okada, BA, Research Assistant:*** **Ms. Okada is a Senior Researcher and Microbiologist at Sunstar Inc. in Japan. She is currently a Research Scholar in the School of Dental Medicine at UB. She has worked on laboratory and clinical studies, especially microbial and immunological analyses for evaluation of oral care products and functional materials. She has training in culturing techniques and bacterial identification. More recently she has investigated the oral microbiome in subjects with specific conditions such as dry mouth, cancer and diabetes by using 16S rRNA gene sequencing, and also conducted randomized clinical trials on the effects of a mouthwash containing antibiotics for gingivitis and the effects of probiotics for hypo-salivation. Ms. Okada will contribute to developing the protocol and study procedures, and microbiome and statistical analyses. Ms. Okada is well qualified to be a Research Assistant of this study. She has completed all IRB-required CITI training and a conflict of interest management plan was developed and completed.**

**Dental Assistant: TBN, they will be CITI trained and added to Click as a Study Team Member via a Modification once they are selected.**

***Describe other resources available to conduct the research.***

*14.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.*

*NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.*

Response: **The PI and Investigator will contribute approximately 5% effort to this study.**

*14.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.*

*NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.*

Response:

**All staff are trained in CPR and procedures are in place for emergencies. The School of Dental Medicine is also available for referrals for dental needs and referrals not addressed in the study.**

*14.4 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.*

Response: **We have extensive training sessions with staff reading the protocol, Informed Consent and all procedural SOPs before and after the training sessions. Examiners are calibrated to the Gold Standard Examiner, consistency of exams is checked, and examination of the data is completed regularly every six months. These training sessions will be documented using a Training Log (included in the revised IRB package #3). All staff who consent participants must demonstrate to a PI representative skilled in correct consenting procedures before they can consent "real" participants. Updates are provided and checks made of proficiency as needed and yearly.**

## 15.0 Other Approvals

*15.1 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).*

Response:

☒ **N/A:** This study does not require any other approvals.

## 16.0 Provisions to Protect the Privacy Interests of Subjects

*16.1 Describe how you will protect subjects' privacy interests during the course of this research.*

*NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.*

*Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."*

Response:

**Potential and enrolled participants will interact with the study staff, dentists, registered dental hygienists, dental assistants, laboratory technicians, research associates and data manager. Participants may choose not to answer questions, but if those questions provide critical information needed to answer the research questions, the person will not be allowed to remain in the study. When exams are performed, privacy is provided via individual examination rooms; when participants have samples such as saliva and plaque collected, they are provided privacy from the view of others; blood is collected and height and weight measured out of the view of others as well.**

**Participants are told they may withdraw from the study at any time with no adverse effects on them. They are told we need certain data and that data need is explained prior to enrollment (at the time of consenting).**

*16.2 Indicate how the research team is permitted to access any sources of information about the subjects.*

*NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question **does apply** to records reviews.*

Response: **Consent of the participant.**

## 17.0 Data Management and Analysis

*17.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.*

Response:

***16S rRNA Microbiome Sequencing:*** **Samples will be analyzed to determine their bacterial composition using MiSeq (Illumina, Inc.) metagenomic sequencing technology, which is available through the Next-Generation**

**Sequencing and Expression Analysis Core Laboratory. This method can evaluate the bacterial composition of the microbiome, including those not previously cultivated. We will sequence V4 hyper-variable region of the 16S rRNA gene specific for bacterial analyses. Briefly, bacterial DNA will be isolated from all samples and will be processed by polymerase chain reaction (PCR) with control samples into sequencing libraries compatible with the MiSeq sequencer. There are techniques to tag specific samples so that every participant sample can be independently characterized. We will incorporate quality assurance checks on the microbiome analyses by using standardized mock plaque and other sample controls containing known oral organisms, as well as standard reagent control samples and negative controls. We will process the control samples with participant samples using the same procedures to determine if any bias is introduced in the DNA preparation, amplification or sequencing procedures. DNA isolation and PCR development of libraries for sequencing will be carried out using microbiome optimized, clean technique and microbial free reagents.**

***16S rRNA Sequence Analysis:*** **Methods for microbial composition analysis will follow the general approaches described by Caporaso[9] and Sun[10] relying on two separate strategies, taxonomy-independent and -dependent analyses. Taxonomy-independent analysis provides a basic description of the bacterial composition defined in operational taxonomic units (OTU), while taxonomy-dependent analysis relates the bacterial composition (OTU data) to known bacterial classifications defined by shared characteristics of bacterial groups (taxonomy). This two-pronged approach allows analysis of known bacteria using reference databases and discovery of unknown bacteria in the sample. This aspect of the MiSeq sequence analysis allows for more complete characterization of bacterial composition than older available technology used in previous studies.**

**Prior to either analysis, the data will be pre-processed for error-correction to remove low quality reads[9]. A BLAST search will assign sequences to known reference sequences using regularly updated databases[10]. Analyses will be performed to group sequences into an OTU table using computational methods developed by members of our group[10]. The OTU table provides a global view of the bacterial composition comprising the microbiome. The 2000-processor Dell P4 (64-bit) Linux cluster at UB's Center for Computational Research (CCR) can process the large quantity of data generated in this pilot project.**

***Data Analysis:*** **Statistical procedures will be limited to descriptive analyses in this pilot study. Following the 16S rRNA sequencing and data reduction steps, we will describe the subgingival microbiome composition and relative abundance (OTU table). To begin to understand potential differences in the groups, univariate statistical analysis and descriptive statistics will be performed to identify oral bacteria associated with diabetes status and treatment group. Numerical, graphical (boxplots, scatterplots), and formal**

**comparisons (Student's t-test, ANOVA, regression, or non-parametric equivalents for sparse bacteria) will be produced for visualization of results. Other analytic techniques will be utilized as well[10].**

**Descriptive statistics as well as univariate statistical analysis will be performed to identify oral bacteria associated with diabetes status and treatment group. Multivariable logistic regression will be conducted to control for other risk factors. Principal Component Analysis (PCA) or Hierarchical Cluster Analysis (HCA) also will be used to further understand potential associations with diabetes status and treatment group.**

**The analyses planned for this pilot study will provide preliminary data for preparation of a larger more definitive study.**

*17.2 If applicable, provide a power analysis.*

*NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.*

Response:

**A minimum of 104 subjects will be enrolled in the study, with at least 26 participants per group. The study was powered to detect a difference in probing pocket depth (PPD) of 35% between groups, and a standard deviation (SD) of 0.5 for the distribution of 6 month changes. A sample size of 24 per group was estimated assuming approximately 80% power (alpha = 0.05). A minimum 26 subjects per group with an attrition rate of 10% will be enrolled in this study.[17]**

**10-14-2021: We are continuing recruitment to greater than 100 participants in order to balance the numbers of participants per cell, to increase the size of the control group (no perio disease and no diabetes), and to increase the numbers with diabetes but no perio disease so that we have a more solid base on which to complete vigorous data analyses.**

*17.3 Describe any procedures that will be used for quality control of collected data.*

Response: **Double entry of data collected, for example clinical measurements and demographic information, will also be completed and compared for accuracy, and discrepancies will be resolved prior to data analysis.**

**Samples will be selected and testing results reported by laboratory number only. Laboratory number can be linked to ID number from limited-access study files with the linkage data stored on password protected computers.**

**Procedures are in place for quality control of the 16S sequencing and for data analysis.**

## 18.0 Confidentiality

## A. Confidentiality of Study Data

*Describe the local procedures for maintenance of confidentiality of **study data and any records that will be reviewed for data collection**.*

*18.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) **and** electronic files.*

Response:

**Paper records are kept in locked cabinets and/or in locked rooms in 120 and B20 Foster Hall. Computerized data sets are stored in study computers accessible only to authorized study personnel and are password protected.**

**Identity is coded and is not/will not be associated with any published results. Code number and identity will be kept in secured files of the Principal Investigator (see above). The only way participant identity would be revealed is through an on-site review, by an IRB representative, of clinical records to assess the accuracy and consistency with study/research records. S/he might see a name with other information, but they would not be allowed to take any clinical record with a name on it out of the secured area unless mandated by a judicial court. HIPAA policies and practices will be followed in the handling of patients' dental records and study documents.**

**Identifying data are kept in files separate from study data files for as long as there is any interest in re-contacting participants, such as for a follow-up study of some kind.**

**If data files will be used by others outside of the IRB-approved study group, the data files will be the modified to include only identifiers permitted in the "de-identified" classification: gender, ethnicity, age (up to 89 years), year of birth and the first three digits of the zip code as long as the certification of de-identification criteria are met. Additional address information, telephone numbers, email addresses, social security numbers will not be included. We do not collect insurance data, vehicle identifiers, device identifiers, URLs, IP address numbers, voice or finger prints, or photos of participants so they will not be included in the saved data files.**

**All study staff are trained in all study procedures and must receive all training required of the Institutional Review Board at UB and School of Dental Medicine. All data files are stored on password-protected computers and access to those computers is limited to authorized study staff only.**

**Study/research files will be kept by identification (ID) number only. Laboratory numbers are different than ID numbers and the linkage will be stored in limited access files on password-protected computers.**

**Informed Consents are kept separate from study/research charts in limited access (locked) rooms.**

*18.2 A. How long will the data be stored?*

Response: **Until analyzed or indefinitely.**

*18.3 A. Who will have access to the data?*

Response: **Authorized study staff.**

*18.4 A. Who is responsible for receipt or transmission of the data?*

Response: **The PI or authorized PI representative.**

*18.5 A. How will the data be transported?*

Response: **Data will be transported on CDs or flash drives in password protected files. If needed, the CDs can be sent via USPS, FedEx or UPS for data transfer to a more distant person.**

## B. Confidentiality of Study Specimens

*Describe the local procedures for maintenance of confidentiality of **study specimens**.*

☐ **N/A:** No specimens will be collected or analyzed in this research. *(Skip to Section 19.0)*

*18.6 B. Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.*

Response: **Samples are labeled with participant study number, sample number, type of sample, study visit, date and study. Only authorized study personnel handle samples.**

**Samples will be stored, by study, in -80° C freezers in B20 Foster Hall until tested. These rooms are locked, and access is limited to authorized study staff. All freezers are monitored daily for temperature and are on a University alarm system in case they fail.**

*18.7 B. How long will the specimens be stored?*

Response: **Until tested or indefinitely.**

*18.8 B. Who will have access to the specimens?*

Response:

**Authorized study personnel.**

*18.9 B. Who is responsible for receipt or transmission of the specimens?*

Response:

**Authorized study personnel.**

*18.10 B. How will the specimens be transported?*

Response:

**Samples and data will be labeled and identified only by ID number. Samples will be transported frozen on dry ice unless the frozen state is not needed. Data will be housed on limited-access password-protected computers backed up by UB systems. If needed, data will be copied onto CDs and sent via USPS, FedEx or UPS.**

## 19.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

***NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.***

*19.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.*

Response:

**Data collected during the study will be reviewed by the PI and investigators (primarily for clinical issues). These reviews will take place after six months of participant recruitment and every six months thereafter.**

*19.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.*

Response: **Study accrual, reports of adverse and serious adverse events and unanticipated problems will be reviewed by the investigators.**

*19.3 Describe any safety endpoints.*

Response:

**Adverse and serious adverse events, untoward events will be assessed by asking about changes in status and new events since last visit.**

*19.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).*

Response: **When subjects return for study visits, they will be queried about changes in their medical and dental status, untoward events, new medications etc. This information will be recorded on study visit checklists and progress notes and used when data are reviewed by the PI, investigators and study staff.**

*19.5 Describe the frequency of safety data collection.*

Response: **Data will be collected at the study visits and will start at the beginning of the study.**

*19.6 Describe who will review the safety data.*

Response: **The PIs and Investigators, coordinator.**

*19.7 Describe the frequency or periodicity of review of cumulative safety data.*

Response:

**After six months and every six months thereafter.**

*19.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.*

Response: **All adverse events (serious and non-serious) reported during a study will be taken into account when analyzing study data, and will be included in the final study report. Identification of serious adverse effects (SAEs) will be used to identify, during the conduct of the study, those adverse events that may require an expedited reporting procedure to regulatory authorities. No testing of drugs will be used. Therefore, statistical tests will be used to evaluate SAEs only if events are serious.**

*19.9 Describe any conditions that trigger an immediate suspension of the research.*

Response:

**Faulty equipment and mass terminations of staff, for example.**

## 20.0 Withdrawal of Subjects

☐ **N/A:** This study is not enrolling subjects. This section does not apply.

*20.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.*

Response: **If it is not in the best clinical interest of the participant or if the participant is unable to comply with study requirements, s/he will be withdrawn from the research, and notified of such withdrawal. This will be determined by the PI, investigators and coordinator.**

*20.2 Describe any procedures for orderly termination.*

*NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.*

Response: **Inform the participant verbally and document in chart progress notes.**

*20.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.*

Response: **Participants will be asked if they wish to withdraw from all components of the study or if they will allow follow-up activities. For observational studies such as this one, withdrawal is not likely, but participants who want to withdraw will be asked if any samples already collected may be used in the research. If participant does NOT want those samples used, those samples will be destroyed.**

## 21.0 Risks to Subjects

*21.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.*

*NOTE: Breach of confidentiality is always a risk for identifiable subject data.*

Response: **None of the study procedures (e.g., oral health examination, periodontal measurements, collection of biological specimens) are considered experimental. They are all considered standard of care. Known possible risks of participating in this study are described below. As with all clinical procedures, this study may also involve unforeseen risks to participants.**

**<u>Periodontal Examination</u>: The periodontal examination will involve procedures that are routine in dental practice. A licensed dentist or dental hygienist will perform the procedures. The risks from the periodontal examination include minor discomfort or pain during and**

**after the procedures and minor bleeding, inflammation, and swelling of the gums.**

**Collection of Samples from the Mouth: During the study, we will take samples of saliva and plaque. The saliva will be collected by having participants spit into a container. Both of these procedures have very little risk. Collecting plaque samples has a small risk of causing minor bleeding of the gums. This risk is low because all the examiners are experienced and skilled in proper collection technique.**

**Blood Sample Collection: Blood samples will be drawn by trained and experienced health care personnel. There may be some discomfort and bruising at the site where the needle enters the skin, and there is a very small risk of fainting. Infection in the area of needle insertion is rare.**

**Vaginal Swab Sample Collection: There is little risk to the participant in collecting vaginal swabs.**

**Stool Collection: There is little risk to the participant in collecting a stool sample. Specific instructions and supplies will be provided to minimize mess and unpleasantness.**

**Dental radiographs: About 18 radiographs will be taken. These x-rays will not be taken if suitable x-rays taken in the past two years are available to review, or if the dental clinician feels there is no clinical need for them. The amount of radiation exposure from the dental x-rays in this study is about 17.1 millirem (or 0.017 rem). This amount is below the 5 rem per year allowed for research participants by the National Institutes of Health (NIH) Radiation Safety Committee. The average person in the United States has a radiation exposure of about 0.36 rem per year from natural sources, such as the sun, outer space, and earth's air and soil. When taking x-rays, the lowest dose possible will be used and participants will wear a lead apron to reduce exposure.**

**Although there is no direct evidence that the amount of radiation exposure from participating in this study is harmful, there is indirect evidence that it may not be completely safe. There may be a very slightly increased risk of cancer.**

**Paroex® is a non-alcohol chlorhexidine preparation. With use of chlorhexidine, there is risk of reversible staining of teeth and the possibility of some alteration in taste. There is increased likeliness of staining in smokers, coffee drinkers and those who are susceptible to teeth staining in general. The cleaning of the front teeth that will be**

**provided at the 3-month visit will help to reduce any staining that may occur. If there is any alteration in taste, it should go away when use of chlorhexidine stops. Paroex®was approved by the FDA November 29, 2005 (application # (ANDA) 076434).**

**Soft-Picks may cause some bleeding of the gums at first usage, but the bleeding should lessen and stop as use is continued (as gums heal). Soft-Picks are a readily available consumer product sold in supermarkets and drug stores. They are "510(k) exempt" from requiring FDA approval.**

**Taste Test: There is minimal risk to taking the Taste Test.**

*21.2 Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.*

Response: **See above (21.1), well trained and experienced study staff, and below.**

**The electronic data files for study data do NOT include general identifiers except study Identification (ID) number. Examples of these files are Medical History file, Dental History file, medications file, blood testing results, periodontal examination data file where the results of the clinical examination are recorded and saved by ID number only. These files do not have names or other contact information though the medical history file does have date of birth (DOB). One study file has demographic information needed to identify participants and for communications and correspondence with the participants (names, address information, telephone numbers, email addresses). Another file has gender, ethnicity, age (up to 89 years), year of birth and the first three digits of the zip code by study ID number. Social security numbers are obtained for reimbursement purposes as required by Research Foundation, but are not included in data files. We do not collect insurance data, vehicle identifiers, device identifiers, URLs, IP address numbers, voice or finger prints, or photos of participants so they will not be included in the saved data files.**

*21.3 If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.*

Response: **Unknown.**

*21.4 If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.*

Response: **None known.**

*21.5 If applicable, describe risks to others who are not subjects.*

Response: **None known.**

## 22.0 Potential Benefits to Subjects

*22.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.*

*NOTE: Compensation **cannot** be stated as a benefit.*

Response: : **Participants will gain information about the results of their laboratory blood tests, the health and status of their mouths, as well as information about their periodontal status and degree of periodontal disease. They will also receive a copy of their radiographs, if they wish.**

**Participants will receive treatment and monitoring of their periodontal disease for one year, a significant benefit to their oral health. If they do not respond to the standard study treatments either SRP alone of SRP + SPT, they will receive additional treatment (Rescue Therapy) that will be determined by the study dentist(s)/periodontist(s)). Blood for fasting glucose, hemoglobin $A_{1c}$, insulin, and hs-CRP will be measured during the study and results will be shared with participants thereby providing them with status updates.**

## 23.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

*23.1 **If the research procedures carry a risk of research related injury,** describe the available compensation to subjects in the event that such injury should occur.*

Response: **Risk is minimal. See below contract language regarding Sunstar Inc responsibility.**

Sponsor agrees to reimburse Institution for the reasonable and necessary costs of medical treatment provided in the event that a Study subject sustains a physical injury or illness as a direct result of the use of a Study Drug/Device, or performance of any procedure required by the applicable Protocol, provided that: (i) the Study Drug/Device or required procedure was administered in accordance with the applicable Protocol and any other written instructions provided to Institution by Sponsor; and (ii) the injury was not caused by the negligence or misconduct of Institution or Personnel. Further, Sponsor shall not be responsible for any such medical treatments that are due to disease progression, pre-existing medical conditions or underlying disease (whether previously diagnosed or not). The obligations described in this Section 18 (Subject Injury) shall survive the expiration or earlier termination of this Agreement.

*23.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.*

*NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with **different language regarding research related injury**, you must modify your response here and submit an amendment to the IRB for review and approval.*

Response: **See above, 23.1**

## 24.0 Economic Burden to Subjects

*24.1 Describe any costs that subjects may be responsible for because of participation in the research.*

*NOTE: Some examples include transportation or parking.*

Response: **We do not anticipate any added expenses for participants beyond those needed to attend study visits. Anticipated expenses for participants are the cost of transportation to and from the study center, cost of meals while at the study center (if needed; we provide light snacks such as muffins, breakfast bars, coffee, and juice), and cost of lodging if an overnight stay is required for the study visit (the latter is not likely because recruitment is local and most participants in previous studies have lived nearby). Groups A and B will have the products, Paroex® and Soft-Picks, provided.**

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

## 25.0 Compensation for Participation

*25.1 Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.*

Response: **$50 each for Baseline, 3-month, 6-month and 9-month visits; $100 for 12-month visit for a total of $300 per participant.**

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☐ **N/A:** There is no compensation for participation. This section does not apply.

## 26.0 Consent Process

*26.1 Indicate whether you will be obtaining consent.*

*NOTE: This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study. Consent documentation is addressed in Section 27.0.*

☒ ***Yes*** *(If yes, Provide responses to each question in this Section)*

☐ ***No*** *(If no, Skip to Section 27.0)*

*26.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.*

Response: **An operatory in the PDRC.**

*26.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.*

*NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.*

Response: **Subjects will be given the opportunity to ask as many questions as they need to be comfortable prior to signing the consent form. Subjects will be asked to provide or decline consent within 24 hours of having the study explained in detail.**

*26.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.*

Response: **If a participant presents for a study visit we assume they are consenting to continue in the study; however, we will add a question to our study visit checklists asking, "Participation in this study is voluntary. Do you continue to consent to being in this study?" to make sure there is not confusion regarding continuing consent to participate in a research study. If it is the first visit, the first thing we do is obtain consent. As we proceed through the first, and all visits, we ask the question above. At the end of the first visit, we make the appointment for the second visit and we also make a reminder phone call the day or two before the second visit. We usually speak to the participants during the call so they again have the opportunity to say they do not want to continue or they need a new appointment date and/or time.**

**If a participant does not show up for a visit and cannot be reached and continues this behavior, we try to reach them by phone and email and, if no response, eventually by registered mail with a postage-paid envelope so they can send us an answer about continuation. In the past, some participants have had personal or family problems arise and some have continued with adjustment of visit timing; others have chosen to withdraw or we withdrew them.**

**For participants who show up to study visits and do not ask questions about procedures we assume they want to continue. BUT, we will ask the new question and we are sensitive to non-verbal signs of problems and would probe and give extra time for questions, answers and try to solve "issues" if verbal or non-verbal signs of decreased interest or concerns about the study were evident. In addition, when it is time to**

**begin different aspects of the visit, we also say, "Is it OK to begin…?" If they need more time or want to opt out of continuing they can do so then.**

**Subjects who do not show up for two consecutive study visits and are unable to be reached on two different occasions at all contact numbers to remind them of a scheduled follow-up appointment will be deemed uninterested in continued participation and will be considered lost to follow-up.**

*26.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:*

- *The role of the individuals listed in the application who are involved in the consent process*
- *The time that will be devoted to the consent discussion*
- *Steps that will be taken to minimize the possibility of coercion or undue influence*
- *Steps that will be taken to ensure the subjects' understanding*

Response:

☒ We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

***Non-English Speaking Subjects***

☒ **N/A:** This study will not enroll Non-English speaking subjects. *(Skip to Section 26.8)*

*26.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.*

*NOTE: The response to this Section should correspond with your response to Section 6.4 of this protocol.*

Response:

*26.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.*

*NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."*

Response:

***Cognitively Impaired Adults***

☒ **N/A**: This study will not enroll cognitively impaired adults.
*(Skip to Section 26.9)*

*26.8 Describe the process to determine whether an individual is capable of consent.*

Response:

***Adults Unable to Consent***

☒ **N/A**: This study will not enroll adults unable to consent.
(*Skip to Section 26.13)*

*When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 26.9 and 26.10)* ***and, where possible, assent of the individual should also be solicited*** *(Sections 26.11 and 26.12).*

*26.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" for research in New York State.*

*NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.*

Response:

☐ We have reviewed and will be following "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

*26.10* ***For research conducted outside of New York State****, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response: **This study will NOT be conducted outside of New York State.**

*26.11 Describe the process for* ***assent of the adults****:*

- *Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.*

Response: N/A.

- *If assent will not be obtained from some or all subjects, provide an explanation of why not.*

Response: **N/A**

*26.12 Describe whether **assent of the adult** subjects will be documented and the process to document assent.*

*NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the "Template Consent Document (HRP-502)" Signature Block for Assent of Adults who are Legally Unable to Consent.*

Response: **N/A**

***Subjects who are not yet Adults (Infants, Children, and Teenagers)***

☒ **N/A**: This study will not enroll subjects who are not yet adults. *(Skip to Section 27.0)*

*26.13 Describe the criteria that will be used to determine **whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research** under the applicable law of the jurisdiction in which the research will be conducted **(e.g., individuals under the age of 18 years)**. For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

*NOTE: Examples of acceptable responses include: verification via electronic medical record, driver's license or state-issued ID, screening questionnaire.*

Response: **N/A**

*26.14**For research conducted outside of New York State**, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response: **N/A**

*26.15 Describe whether parental permission will be obtained from:*

Response: **N/A**

☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

*NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the "CHECKLIST: Children (HRP-416)."*

*26.16Describe whether permission will be obtained from individuals **other than parents**, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.*

Response: **N/A**

*26.17 Indicate whether assent will be obtained from all, some, or none of the **children**. If assent will be obtained from some children, indicate which children will be required to assent.*

Response: **N/A**

*26.18 When assent of children is obtained, describe how it will be documented.*

Response: **N/A**

## 27.0 Waiver or Alteration of Consent Process

***Consent will not be obtained, required information will not be disclosed, or the research involves deception.***

☒ **N/A:** A waiver or alteration of consent is **NOT** being requested.

*27.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.*

*NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.*

Response: **N/A**

*27.2 If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:*

Response: **N/A**

## 28.0 Process to Document Consent

☐ **N/A:** A Waiver of Consent is being requested.
*(Skip to Section 29.0)*

*28.1 Indicate whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.*

*NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent. This is sometimes referred to as 'verbal consent.' Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information.*

*If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).*

Response:

**All study staff will be trained in the Informed Consent process through in-service programs, demonstrations, practice sessions, and demonstrations of proficiency to ensure ability to conduct the consenting process properly with prospective participants. Steps that are taken in the Informed Consent process and to minimize the possibility of coercion and undue influence by study personnel include the following:**

**1. An eligibility criterion of this study is to be able to read and sign the consent form so those not able to read the consent will be excluded from the study.**

**2. Discuss and explain study with potential participants.**

**3. Have potential participant read Informed Consent form.**

**4. Allow as much time as needed for questions.**

**5. Answer questions; make sure the person has his/her questions answered to his/her satisfaction, and so they understand the study.**

**6. Make sure the potential participant understands the number of study visits required, how long those appointments last and the total time commitment of the study for them.**

**7. The Informed Consent form must be signed prior to ANY study procedures. In addition, each page must be initialed indicating that participant read that page.**

**8. Informed Consent should be signed by the person obtaining consent, the PI or his/her designee.**

**9. Make sure the HIPAA consent is also signed. It may be attached to or be a separate document from the study consent.**

**10. Give copy of signed Informed Consent to participant.**

**The time involved in the consenting process is approximately 15 to 30 minutes.**

☒ We will be following "SOP: Written Documentation of Consent" (HRP-091).

## 29.0 Multi-Site Research (Multisite/Multicenter Only)

☒ **N/A:** This study is not an investigator-initiated multi-site study. This section does not apply.

*29.1 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as:*

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*

- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response: **N/A**

*29.2 Describe the method for communicating to engaged participating sites:*

- *Problems*
- *Interim results*
- *Study closure*

Response: **N/A**

*29.3 Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.*

Response: **N/A**

*29.4 If this is a multicenter study for which UB will serve as the IRB of record, and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods.*

Response: **N/A**

## 30.0 Banking Data or Specimens for Future Use

☐ **N/A:** This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

*30.1 If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

*NOTE: Your response here must be consistent with your response at the "What happens if I say yes, I want to be in this research?" Section of the Template Consent Document (HRP-502).*

Response: **Saliva, blood, plaque, skin and vaginal swabs, and feces will be stored in -80º C freezers in B20 Foster Hall until tested or indefinitely. The samples will be stored by sample number with a central inventory kept for all freezer contents. Freezers are maintained in locked rooms (B20 Foster Hall is a suite of rooms) with access limited to authorized study staff. All freezers are on the University alarm system and are checked regularly for temperature.**

**Study data may also be kept indefinitely. Paper files are kept in the PDRC, a suite of rooms in 120 and B20 Foster Hall, with study files identified only by study ID number, stored separately from clinical files with names and other identifying information. All electronic study data are stored on password-protect computers in locked rooms in the PDRC, and able to be accessed by authorized study staff only.**

*30.2 List the data to be stored or associated with each specimen.*

Response: **Laboratory number, specimen type, date of collection, amount and study. In addition, if samples are removed, thawed and portions removed, this information is noted in the central inventory system. These data will be stored on password-protect computers in locked rooms in the PDRC, and able to be accessed by authorized study staff only.**

*30.3 Describe the procedures to release banked data or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.*

Response: **All requests for samples or data must be preceded by submitting a brief proposal to the PIs who will share it with other study investigators. Proposals will need project description, rationale, main hypotheses and/or purposes, what is needed, (samples, for example, type and how they will be used or tested; and data, variables desired, dependent and independent), a brief summary of the analytic plan, and a description of how the samples and/or data are to be handled and confidentiality maintained.**

**Study investigators and the PIs will evaluate proposals and consider the propriety, priority, cost, and ease of obtaining the samples and/or data and advise the lead author accordingly. If approved for data requests, documentation and data files will be created by the data manager and sent to the requestor by the PIs. Only data identified by study ID will be shared. The data manager will define variables including derived variables and verify data as needed. For transfer of data, CDs or flash drives will be used for transfer.**

**For samples, costs associated with retrieval, maintenance during transport, and shipping will be determined. Dates and times of preparations and shipping or transport will be determined by the PIs and requestor precisely to maintain the integrity of the samples.**

## 31.0 Drugs or Devices

☐ **N/A:** This study does not involve drugs or devices. This section does not apply.

*31.1 If the research involves drugs or devices, list and describe all drugs and devices used in the research, the purpose of their use, and their regulatory approval status.*

Response: **Paroex® mouthrinse, FDA approved and used according to labeling. Soft-Picks, 510(k) exempt and available over the counter.**

Here are the links: **Paroex®: http://us-professional.gumbrand.com/gumr-chlorhexidine-gluconate-oral-rinse-4.html**

**Soft-Picks: http://www.sunstar.com/rd/story/soft-picks-advanced; http://www.gumbrand.com/gum-soft-picks-40-ct-632rc.html; and http://www.soft-picks.com/about-soft-picks.**

*http://us-professional.gumbrand.com/gumr-chlorhexidine-gluconate-oral-rinse-4.html*

Sunstar, Inc. has ownership of these products.

*31.2 Describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.*

Response: **Paroex® and Soft-Picks will be stored in our limited access, locked cool room adjacent to the PDRC.**

***If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:***

*31.3 Identify the holder of the IND/IDE/Abbreviated IDE.*

Response: **The Paroex® mouthrinse and Soft-Picks to be used in this study are not investigational. Paroex® mouthrinse is FDA approved and will be used according to labeling. Soft-Picks are like small tooth brushes and are readily available over the counter.**

*31.4 Explain procedures followed to comply with FDA sponsor requirements for the following:*

| | *Applicable to:* | | |
|---|---|---|---|
| ***FDA Regulation*** | ***IND Studies*** | ***IDE studies*** | ***Abbreviated IDE studies*** |
| ***21 CFR 11*** | ***X*** | ***X*** | |
| ***21 CFR 54*** | ***X*** | ***X*** | |
| ***21 CFR 210*** | ***X*** | | |
| ***21 CFR 211*** | ***X*** | | |
| ***21 CFR 312*** | ***X*** | | |
| ***21 CFR 812*** | | ***X*** | ***X*** |
| ***21 CFR 820*** | | ***X*** | |

Response: **N/A**

## 32.0 Humanitarian Use Devices

☒ **N/A:** This study does not involve humanitarian use devices. This does not apply.

*32.1 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.*

Response:

*32.2 For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.*

Response: