Complete Research Protocol (HRP-503)

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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 Example
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: Clinical evaluation of the efficacy of an intra oral rinse for patients with xerostomia

PRINCIPAL INVESTIGATOR:

Name
Department
Telephone Number
Email Address

Response: Sebastian G. Ciancio, D.D.S.

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VERSION NUMBER/DATE:

Include the version number and date of this protocol.

Response: version 02, Date: 04/21/2020

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
#1	4/21/2020	Changes made per IRB deferral comments	yes
#2	5/13/2020	Changes made per IRB comment	yes

FUNDING:

Indicate any funding for this proposal. This should match the Funding Sources page in Click IRB.

Response: This project is funded by Sunstar America.

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: This project is not funded by a Grant.

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:

Location: 250 Squire Hall

Address: School of Dental Medicine, University at Buffalo, Buffalo, NY 14214

Department: Department of Periodontics and Endodontics

1.0 Study Summary

Study Title	Clinical evaluation of the efficacy of an intra oral rinse for patients with xerostomia
Study Design	Randomized, double –blind, placebo controlled cross over study
Primary Objective	1. To evaluate patients' perception of efficacy of a new currently marketed mouth rinse (HYDRAL) for xerostomia compared to a placebo mouth rinse (negative control) and another currently marketed mouthrinse (Biotene) in reducing the symptoms of xerostomia. 2. To determine the efficacies on dry mouth relief and on the patient's Quality of Life (QoL) at the beginning and end of the study.
Secondary Objective(s)	1. To objectively evaluate the improvement of dry mouth symptoms by HYDRAL compared to the placebo and Biotene. 2. To evaluate the safety of the test mouthrinse on teeth and oral soft tissues. 3. To evaluate the patient's preferences relative to the test mouthrinses.
Research Intervention(s)/ Investigational Agent(s)	Mouth rinse (HYDRAL)
IND/IDE #	N.A

Study Population	Adults males and females
Sample Size	39
Study Duration for individual participants	8 weeks
Study Specific Abbreviations/ Definitions	

2.0 Objectives*

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

Response: The objectives of this randomized double -blind placebo controlled cross over study are:

1) To evaluate patients' perception of efficacy of a new mouth rinse (HYDRAL) for xerostomia compared to a placebo mouth rinse (negative control) and another mouthrinse (Biotene) in reducing the symptoms of xerostomia.
2) To determine the efficacies on dry mouth relief and on the patient's Quality of Life (QoL) at the beginning and end of the study.
3) To objectively evaluate the improvement of dry mouth symptoms by HYDRAL compared to the placebo and Biotene.
4) To evaluate the safety of the test mouthrinse on teeth and oral soft tissues.
5) To evaluate the patient's preferences relative to the test mouthrinses.

2.2 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) HYDRAL performs as well as or better than Biotene in reduction of the symptoms. HYDRAL performs better than the placebo rinse in reduction of the symptoms.
2) HYDRAL improves patient's quality of life as well as or better than Biotene. HYDRAL performs better than the placebo rinse in improvement of patient's Quality of Life (QoL)

3.0 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.*

Response: The primary endpoint is a reduction of dry mouth symptoms

4.0 Background*

4.1 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: Currently, the prevalence of dry mouth varies widely among the general population. When asked, 14–46% of the adult population complains about dry mouth problems, women more than men [1]. Xerostomia is generally defined as a subjective feeling of dry mouth, often the result of hyposalivation caused by different medical issues. All grades of xerostomia may impact on oral health and quality of life [2]. Long-term causes of hyposalivation include chronic diseases (diabetes, Sjögren's syndrome, Parkinson's disease, rheumatoid arthritis, etc.), illness of the parotid glands, malignancies in the head and neck region and their treatment, as well as head and neck surgery or anamnestic radiation. Another underrated main cause of xerostomia in the general population is medication-induced xerostomia [3]. Older age in combination with a large number of prescribed drugs ranks as an important activator for xerostomia [4–6]. The clinical oral effects of xerostomia are many and include difficulties in speaking, swallowing or eating, a reduced or altered taste sensation, atrophy of mucosal tissue with pain, demineralization of the teeth, and often occurrence of secondary infections of oral tissues [7].

Yet there is almost no evidence in the literature regarding treatment of this special patient population with medication-induced xerostomia with symptom-relieving products, or evidence-based guidelines as to which products can be recommended to patients and how effective they are [8]. The efficacy of therapies is mainly described in populations with post-radiotherapy xerostomia [9–13]. In this study, we intend to investigate and compare the efficacy of GUM Hydral and Biotène Oral balance.

4.2 Include complete citations or references.

Response:

[1]. Sreebny LM (2000) Saliva in health and disease: an appraisal and update. Int Dent J 50:140–161

[2]. Davies AN (2000) A comparison of artificial saliva and chewing gum in the management of xerostomia in patients with advanced cancer. Palliat Med 14:197–203

[3]. Nederfors T, Isaksson R, Mornstad H, Dahlof C (1997) Prevalence of perceived symptoms of dry mouth in an adult Swedish

population relation to age, sex and pharmacotherapy. Community Dent Oral Epidemiol 25:211–216

[4]. Bardow A, Nyvad B, Nauntofte B (2001) Relationships between medication intake, complaints of dry mouth, salivary flow rate and composition, and the rate of tooth demineralization in situ. Arch Oral Biol 46:413–423

[5]. Locker D (1995) Xerostomia in older adults: a longitudinal study. Gerodontology 12:18–25

[6]. Villa A, Abati S (2011) Risk factors and symptoms associated with xerostomia: a cross-sectional study. Aust Dent J 56:290–295. doi: 10.1111/j.1834-7819.2011.01347.x

[7]. Epstein JB, Stevenson-Moore P (1992) A clinical comparative trial of saliva substitutes in radiation-induced salivary gland hypofunction. Spec Care Dentist 12:21–23

[8]. Barbe AG, Bock N, Derman SH, Felsch M, Timmermann L, Noack MJ (2016) Self-assessment of oral health, dental health care and oral health-related quality of life among Parkinson's disease patients. Gerodontology. doi:10.1111/ger.12237

[9]. Kirstila V, Lenander-Lumikari M, Soderling E, Tenovuo J (1996) Effects of oral hygiene products containing lactoperoxidase, lysozyme, and lactoferrin on the composition of whole saliva and on subjective oral symptoms in patients with xerostomia. ActaOdontol Scand 54:391–397

[10]. Kirstila V, Lenander-Lumikari M, Tenovuo J (1994) Effects of lactoperoxidase-system-containing toothpaste on dental plaque and whole saliva in vivo. Acta Odontol Scand 52:346–353

[11]. Kielbassa AM, Shohadai SP, Schulte-Monting J (2001) Effect of saliva substitutes on mineral content of demineralized and sound dental enamel. Support Care Cancer 9:40–47

[12]. Warde P, Kroll B, O'Sullivan B, Aslanidis J, Tew-George E, Waldron J, Maxymiw W, Liu FF, Payne D, Cummings B (2000) A phase II study of Biotene in the treatment of postradiation xerostomia in patients with head and neck cancer. Support Care Cancer 8:203–208

[13]. Epstein JB, Emerton S, Le ND, Stevenson-Moore P (1999) A double-blind crossover trial of Oral Balance gel and Biotene toothpaste versus placebo in patients with xerostomia following radiation therapy. Oral Oncol 35:132–13.

5.0 Study Design*

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

Response: Randomized double -blind placebo controlled cross over study. Randomization-Patients will be assigned to the study product using a random numbers table. Both the placebo rinse and the "active "test rinses" will be provided by the sponsor in similar bottles labeled with a code label for each bottle. The code and patient numbers will be kept in a sealed cabinet in 250 squire Hall. The code will only be broken if there is need to identify a patient with adverse effects which may be attributed to the rinse they were given.

6.0 Study Intervention/Investigational Agent

1.1 Description: *Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated.*

Response: HYDRAL Oral rinse and Biotene rinse contain one or more of the following: Sorbitol, Sodium citrate, Propanediol, Polyvinylpyrrolidone, Betaine, PEG-40 Hydrogenated Castor Oil, Xylitol, Taurine, Citric acid, Sodium hydroxide, Methyl paraben, Flavor, Mild Mint flavor, Sodium hyaluronate, Cetylpyridinium chloride, Sucralose, Stevia Redaudiana Extract, Glycerin, Propylene Glycol, Poloxamer 407, Sodium Benzoate, Hydroxyethyl Cellulose, Propylparaben, Sodium Phosphate, Disodium Phosphate

6.1 Drug/Device Handling: If the research involves drugs or device, 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.

- *If the control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., Research Pharmacy SOP for the Control of Investigational Drugs, etc.), please reference that SOP in this section.*

Response: An inventory of the study products and dispensing logs will be maintained by the Clinical Coordinator. Unused materials will be disposed.

6.2 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:

- *Identify the holder of the IND/IDE/Abbreviated IDE.*
- *Explain procedures followed to comply with sponsor requirements for FDA regulated research 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: The device is not investigational and is in commercial use. The device holds a 510(K) by the FDA (attached in devices section of the IRB submission portal).

7.0 Local Number of Subjects

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

Response: 39

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

Response: We anticipate screening 125 subjects to reach our target sample of 39.

7.3 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?

8.0 Inclusion and Exclusion Criteria

Response: The number of subjects needed for this study is based on the feasibility of the study.*Inclusion and Exclusion Criteria**

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

NOTE: This may be done in bullet point fashion.

Response: Individuals may be included in the study provided they meet all of the following inclusion criteria:

- Must have read, understood and signed an informed consent prior to being entered into the study,
- Must be 18 to 80 years of age, male or female,
- Have at least 20 natural or restored teeth,
- Have a complaint of xerostomia,

- Have an unstimulated salivary flow rate <0.20 ml/minute which represents a significant reduction of normal salivary function, 6)Must have subjective xerostomia symptom: minimum level of 4 on a 10 centimeters Visual Analog Scale (VAS). The question, using a VAS scale, would be" How would you score your dryness on the basis of a scale of 1 to 10?" and on the left would be zero, and on the right would be severe (10). They would have to score a 4 or higher to be in the study. We would ask this same question both before and after the two week usage period,
- Agree not to have a dental prophylaxis or any other elective, non-emergency dental procedures (other than those provided during the study) any time during the study,
- Agree to abstain from the use of any products for xerostomia other than those provided in the study
- Agree to comply with the conditions and schedule of the study.

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

NOTE: This may be done in bullet point fashion.

Response: Individuals are not eligible for participation in this study if any of the following are noted:

- Physical limitations or restrictions that might preclude normal tooth brushing.
- Evidence of gross oral pathology, including widespread caries or chronic neglect, extensive restoration, pre-existing gross plaque or soft or hard tissue tumor of the oral cavity.
- Presence of severe gingivitis with 30 or more sites showing bleeding on probing.
- Evidence of major oral hard or soft tissue lesions or trauma at the baseline visit as determined by the Investigator/Examiner.
- Chronic disease with concomitant oral manifestations other than xerostomia
- Conditions requiring antibiotic treatment prior to dental prophylaxis and invasive procedures, such as heart murmur, history of rheumatic fever, valvular disease or certain prosthetic implants.
- History of hepatic or renal disease, uncontrolled diabetes, or other serious conditions or transmittable diseases.
- Taking concomitant medications which may interfere with oral tissues such as anticoagulants, NSAID's, and those shown to enlarge gingival tissues.

- A positive pregnancy test at visit one would also cause your removal from the study.
- Subjects who are currently undergoing, or require, extensive dental work, orthodontic treatment or periodontal surgery or orthodontic treatment in the preceding 3 months
- Currently using bleaching trays
- History of radiotherapy, head and neck cancer or Sjogren's syndrome.
- History of significant adverse effects following use of oral hygiene products such as toothpastes and mouthrinses.
- Subjects who are nursing, pregnant or plan to become pregnant for the duration of the study.
- Eating disorders
- Recent history of substance abuse
- Participation in other clinical studies within 14 days of screening
- Smoking >10 cigarettes/day
- Chewing tobacco
- Daily use of symptom alleviating products against xerostomia within 7 days of screening.

8.3 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:

☐ Adults unable to consent

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

☐ Pregnant women

☐ Prisoners

8.4 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: Non-English speaking individuals will be included only if adequate translation support can be obtained. We will include a copy of written informed consent to the IRB in a translated format prior to enrolling of a subject who requires translation.

9.0 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.

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

Response:

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

9.2 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.

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

Response:

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

9.4 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").

*9.5 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.

*9.6 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: N/A

10.0 Eligibility Screening*

*10.1 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: Seven days before screening visit potential subjects shall be advised to stop using their usual dry mouth remedy. Since some mouthrinses and other oral hygiene products have a residual effect on oral tissues, we are asking the potential subjects to cease using these products for one week prior to their visit so that we can evaluate the status of their oral tissues. Male and female subjects will read and sign the informed consent prior to enrollment. Subjects will be asked about demographics, medical history, general health status and current medication usage, and the information will be recorded.

The subjects will be asked if they currently experience any problems such as burning, stinging, irritation, etc., and if so, the nature of the effect, severity and onset time (if known) will be recorded.

VAS scoring of lubrication or moisture of your mouth will be scored and unstimulated saliva flow will be measured (Inclusion Criteria). A qualified dental examiner will perform an oral soft and hard tissue examination (OST) to verify that the subjects meet the inclusion and exclusion criteria.

Following the OST exam, qualifying subject's unstimulated saliva will be collected over a 5 minutes time period and the volume measured to determine if they meet the study criteria for xerostomia. VAS question related to symptoms of xerostomia will be completed (>=4 cm is required for inclusion). Subjects will

also be asked to refrain from eating or drinking for 1 hour prior to being examined.

Upon completion of the screening visit, the Principal Investigator or his designee will review subject screening reports and determine whether or not the subject qualifies for study enrollment. If the subject qualifies, an appointment date will be set for Visit 1 which could be immediately follow the screening exam.

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

11.0 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.

11.1 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:

The study will be advertised in UB dental school clinics and on UB campuses. The subjects will be recruited over a period of approximately 3 months following IRB approval using flyers (uploaded on click IRB) which will be posted in the aforementioned places. The advertisement will also be posted on the UB Dental School website, and UB's Participate in Research Portal. Also, the study team will utilize UB's Clinical and Translational Science Institute for recruitment assistance and consultation.

Patients who are interested in participating will be questioned according to a standard telephone script designed to include inclusion/exclusion criteria (uploaded on click IRB). If eligible to be included, subjects will be invited for a screening exam at the Center for Dental Studies, UB School of Dental Medicine

11.2 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 participants are contacting the research team if interested in participating and are therefore controlling their own privacy interests during recruitment. The center for clinical dental research is a private space that allows data collection while maintaining privacy of the patient. In addition, the data collection, storage, communication and analysis will be carried out in compliance with privacy regulations of University at Buffalo and the School of Dental Medicine.

11.3 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: Flyers will be used for recruitment. These documents have been attached in the IRB submission online. Patients who are interested in participating will be questioned according to a standard telephone script designed to include inclusion/exclusion criteria (uploaded on click IRB). If eligible to be included, subjects will be invited for a screening exam at the Center for Dental Studies, UB School of Dental Medicine.

12.0 Procedures Involved*

*12.1 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: If a potential patient is a mouthrinse user, we will be sending them a Consent Form for the study which they will be asked to read, sign and date and return to us. Also, If they have any concerns or questions, we will discuss with them. Once we receive the signed consent form, we will give patients a screening visit appointment, and remind them to cease use of any mouthrinses for 7 days prior to the appointment. At the screening visit, every potential subject will be consented again and interviewed. Subjects who sign the Informed Consent Form and meet eligibility criteria will then have an Oral Screening Examination by the Primary Examiner. After review of the results of the Informed Consent, Screening Interview and Screening Oral Examination, the Principal Investigator or designee will determine whether or not a subject should be enrolled in the study.

Screening

Seven days before screening visit potential subjects shall stop using their usual dry mouth mouthrinse as outlined above.. Male and female subjects will again read and sign the informed consent with a staff member of the study as a witness.. Since some mouthrinses have a residual effect on oral tissues, we are asking the potential subjects to cease using these products for one week prior to their visit so that we can evaluate the status of their oral tissues . Interested patients will be contacted at least 7 days prior to the screening visit to read, sign and date the Consent Form and then start the one week withdrawal of current mouthrinse

before coming to the screening visit. The study team will then call the patient after the Consent Form is mailed to answer any questions or concerns that they may have. The patient can mail the Consent Form back in a stamped self-addressed envelope. The withdrawal of mouthrinse can begin once the study team receives the Consent Form and notifies the patient of its receipt. Subjects will be asked about demographics, medical history, general health status and current medication usage, and the information will be recorded.

The subjects will be asked if they currently experience any problems such as burning, stinging, irritation, etc., and if so, the nature of the effect, severity and onset time (if known) will be recorded.

VAS scoring of lubrication or moisture of your mouth will be scored and unstimulated saliva flow will be measured (Inclusion Criteria). A qualified dental examiner will perform an oral soft and hard tissue examination (OST) to verify that the subjects meet the inclusion and exclusion criteria.

Following the OST exam, qualifying subject's unstimulated saliva will be collected over a 5 minutes time period and the volume measured to determine if they meet the study criteria for xerostomia. VAS question related to symptoms of xerostomia will be completed (>=4 cm is required for inclusion). Subjects will also be asked to refrain from eating or drinking for 1 hour prior to being examined.

If the patient meets the study criteria and has time to participate in visit 1, they may enter the study following the screening visit. If acceptable for the study, this screening visit will serve as their Visit I baseline.

Visit I

This visit will last approximately 1 hour. The following will happen at this visit: Subjects will be asked to refrain from eating or drinking for 1 hour prior to being examined. If Screening visit and Visit 1 don't happen at the same day, the study staff will update Inclusion/Exclusion Criteria, medical history and concurrent medications.

Subjects will complete VAS question (Appendix A), Xerostomia questionnaire (Appendix B) and Oral Health Impact Profile -14 (OHIP-14) (Appendix C) for the baseline information.

A qualified dental examiner will perform an oral soft and hard tissue examination (OST), unstimulated saliva flow measurement and the objective assessment of oral health condition using the standardized instrument, Revised Oral Assessment Guide (ROAG) (Appendix D). Some intraoral photographs will be taken.

They will then be given their assigned product to use four times daily for two weeks. Subjects will maintain a daily diary (Appendix E) of their product usage and any oral effects they experience and will answer all diary questions. Compliance will be assessed by subject diary and measurement of when unused portion is returned to the clinic.

The subjects will be instructed not to use any other xerostomia products for the duration of the study and to follow their normal oral hygiene procedures. All subjects will be provided with a soft toothbrush and regular fluoride toothpaste to use during the study. Subjects will be scheduled to return in approximately 2 weeks, and will be instructed to refrain from eating and drinking for approximately 1 hour prior to their next visit. They will be advised to follow the instructions carefully and return to the study center with their assigned mouthrinse, and diary after 2 weeks for their next examination. Subjects will receive a reminder call prior to Visit 2.

Visit 2

After 2 weeks, subjects will return to the office to return their dairy. This visit will last approximately 1.5 hour. The following will happen at this visit: The study staff will update of medical history and concurrent medications. Adverse experiences will be noted and recorded during the study.

The study examiner will perform ROAG(Appendix D) to assess the subject's oral health condition.

Subjects will complete VAS question (Appendix A), Xerostomia questionnaire (Appendix B) and OHIP-14 (Appendix C) for after 2 weeks use of the first product. At Visit 2, they will also complete Product Performance and Attributes Questionnaire for the first product (Appendix F).

A qualified dental examiner will perform OST, unstimulated saliva flow measurement and the objective measurement of xerostomia symptoms (Appendix D). Some intraoral photographs will be taken.

Subjects will then remain in the study center for 60 minutes to evaluate whether their mouth feels moist or lubricated, xerostomia relief by questionnaire at 5, 15, 30, 45 and 60 minutes after the in-office use of their assigned product rinse (Appendix G).

Visit 3

After a 1-week washout, subjects will return to the office to begin the second period of the study, using the same study procedures and be assigned the alternate treatment rinse as in Visit 1.

At the end of Visit 4 (examination for the second product) they will go through a 1 week wash out period and then return for Visit 5 (baseline for the third product) and study will be completed in visit 6.

12.2 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: The various data collection points are shown in Table 1 (Study Schedule).

Events	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
		First product		Second product		Third product	
Informed Consent, Demographics, Inclusion/Exclusion Criteria, Medical History, Concurrent meds	X						
Demographics Questionnaire	X						
Oral Soft/Hard Tissue Exam & Photos		X	X	X	X	X	X
Update of Inclusion/Exclusion Criteria, Medical History and Conmeds		X	X	X	X	X	X
Unstimulated saliva flow	X (<0.2)	X	X	X	X	X	X
VAS	X (>=4)	X	X	X	X	X	X
Questionnaires (Xerostomia, QoL)		X	X	X	X	X	X
Objective xerostomia endpoint (ROAG)		X	X	X	X	X	X
Product Distribution		X	X	X	X	X	X
Diary Disbursement		X		X		X	
Compliance Check			X		X		X
Product Attribute Questionnaire			X		X		X
Immediate Post-Rinse Evaluation			X		X		X
Adverse Events			X	X	X	X	X

12.3 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:

a. Demographics Questionnaire
b. Intraoral camera
c. Medical History
d. VAS question (Appendix A),
e. Xerostomia questionnaire (Appendix B)
f. Oral Health Impact Profile -14 (OHIP-14) (Appendix C)
g. Revised Oral Assessment Guide (ROAG) (Appendix D)
h. Daily Diary (Appendix E)
i. Product Performance and Attributes Questionnaire for the first product (Appendix F)
j. Immediate Post-Rinse Evaluation (Appendix G)
k. Oral soft and hard tissue examination form
l. Unstimulated saliva flow measurement form
m. *Adverse Events form*

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

Response: No source records will be used to collect data about subjects.

*12.5 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 data collected in the study will not be shared with the subjects or a third party. The data will be used solely for purposes of this investigation

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

Response: The data collected in the study will not be shared with the subjects or a third party. The data will be used solely for purposes of this investigation. Results post-completion of the study may be published in a de-identified format.

13.0 Study Timelines*

13.1 Describe the anticipated duration needed to enroll all study subjects.

Response: Approximately 3 months will be needed for enrollment.

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

Response: Study duration is approximately 8 weeks and includes 6 visits if the screening is on the same day as visit 1. Each visit is approximately 45 mins to 1.5 hour.

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

Response: 6 months including data analysis.

14.0 Setting

14.1 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: Center for Dental Studies, University at Buffalo School of Dental Medicine. The Center for Dental Studies is a dedicated space for clinical dental investigations.

14.2 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.

15.0 Community-Based Participatory Research

15.1 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.

15.2 Describe the composition and involvement of a community advisory board.

Response:

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

16.0 Resources and Qualifications

*16.1 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: The principal investigator (PI) has extensive experience in clinical dental research. The PI has conducted over 60 clinical trials spanning 45 years. In addition, the support staffs in the study have undergone professional training (including dentistry and dental hygiene) to render dental examinations and care and have collaborated with the PI on multiple projects. The clinical coordinator has been associated with the Center for over 20 years.

Describe other resources available to conduct the research.

16.2 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: PI-2%, Study Coordinator 10%, Study Examiner 16%

16.3 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: If an adverse event occurs, the subject may be scheduled for a follow-up or under the direction of the Principal Investigator referred to a physician or dentist for treatment. Serious Adverse Events will be followed to the extent of resolution possible. Also, Subjects enrolled in the study may elect to withdraw at any time for any reason.

16.4 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: A pre-study briefing will be conducted by the PI with the staff of the Center for Dental Studies to ensure that the study staff understands the design and methodology of the study. Support staff will be encouraged to seek help from the PI if they are concerns/questions related to the study procedures.

17.0 Other Approvals

17.1 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.

18.0 Provisions to Protect the Privacy Interests of Subjects

18.1 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: The clinical dental research center is a dedicated space equipped for private discussions with the patient. This space will be used to collect personal data as it pertains to the study as well as for obtaining informed consent

18.2 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: The research team will collect data, by consent of the subject, as it relates to this study in order to determine if inclusion and exclusion criteria are met. All subject identification will be coded so that the subject's identity is protected Further, clinical data will be used to assess the efficacy and safety of the mouthrinse. Additional sources of data from other healthcare providers will not be accessed.

All subjects will sign and be given a copy of the informed consent agreement The Principal Investigator will maintain the original informed-consent document in the case report folder.

Prior to commencing the study, the Principal Investigator will obtain approval from the Institutional Review Board (IRB) in Compliance with Federal Regulations (21 CFR 56). The IRB will be consulted on the required information for review. Variations or changes in the protocol will not be implemented until approved by the Institutional Review Board.

19.0 Data Management and Analysis*

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

Response: This is a randomized double-blind placebo controlled crossover study comparing the HYDRAL Oral rinse to Biotene rinse, and HYDRAL Oral rinse to placebo. A one-week wash-out period will be adopted between phases to eliminate any possible carry-over effect of a treatment from previous phase. The primary endpoint is a reduction of dry mouth symptom in VAS (0-10 scale). To control for the Type I error rate of incorrectly rejecting the null hypothesis, a two-sided significance level of 0.025 will be used. A power analysis for a crossover study estimated that with 80% power, 33 subjects will be required to detect a minimal difference in mean VAS of 0.8. To account for withdrawal and other factors (e.g. failed measurement), a total of 39 subjects will be recruited and randomized into the study.

Descriptive statistics for all subjects will be performed for background and demographic variables. Continuous variables are expressed as frequencies (n), mean +/- SD and categorical variables are expressed as frequencies (n) and percentages (%). To evaluate the primary end point, an Analysis of variance will be applied to examine the possible residual or carryover effects of treatments. If no residual effect is found, paired t test or Wilcoxon sign-rank test where appropriate, will be used to compare treatments; however, if residual effect is significant, a mixed model (with unstructured covariance matrix) will be performed with treatment, period,

and interaction of treatment and period as fixed effects to account for treatment, period, and carryover effect. For categorical variables, percent or proportion of subjects will be calculated and a Chi-square test or McNemar test will be used. All statistical tests will be conducted using SAS version 9 (SAS Institute Inc. Cary, NC).

19.2 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: The number of subjects needed for this study with adequate power is based on a power analysis of 0.8.

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

Response: The PI and the clinical study member are calibrated in the collection of data required for this study.

20.0 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**.*

*20.1 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: Data (paper records) will be stored at 250 Squire Hall, School of Dental Medicine, University at Buffalo under the control of the PI and will be restricted by a lock-key that can only be accessed by members of the research team on this protocol.

All collected data will be on forms in which the subjects' identity is coded and the code can only be broken if an emergency situation occurs which requires knowledge of the product the subject is using. All data will only be available to study staff and to a biostatistician who will also not know identity. All data will be kept in a locked file cabinet in 250 Squire Hall (PI's office).

All patient identification will be by a coded-key (subject numbers). The code will be stored in a sealed envelope and stored in the PI's locked cabinet (250 Squire Hall). The envelope will not be opened unless required by an emergency situation

related to product use by the patient. This form and all collected data will also be stored in a locked file cabinet in 250 Squire Hall (PI's office). All data collected electronically such as patients evaluations, patient excel log, and patient demographics will be stored in a password protected file on our clinical computer in our Center for Dental Studies.

20.2 A. How long will the data be stored?

Response: The data will be stored for duration of study, data analysis and possible publication (anticipated total of 6 months).

20.3 A. Who will have access to the data?

Response: PI and members of the research team.

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

Response: PI

20.5 A. How will the data be transported?

Response: Data may be transported either through secure paper mail (USPS) or de-identified electronic for statistical analysis (off-site biostatistician).

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)*

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

Response: N/A

20.7 B. How long will the specimens be stored?

Response: N/A

20.8 B. Who will have access to the specimens?

Response: N/A

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

Response: N/A

20.10 B. How will the specimens be transported?

Response: N/A

21.0 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.

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

Response: In addition to the efficacy parameters, safety parameters will be collected by members of the research team. This will ensure a study with minimal risk to the participants and early detection of adverse reactions. If an adverse event occurs, the subject may be scheduled for a follow-up or under the direction of the Principal Investigator referred to a physician or dentist for treatment. Serious Adverse Events will be followed to the extent of resolution possible. The Principal Investigator will note the follow-up and resolution of Adverse Events on the Adverse Events From (uploaded to click IRB). All serious or unsuspected adverse events will be reported to the IRB. Any Serious Adverse Events that occur during the clinical study period will be reported promptly by the Principal Investigator to the IRB within 24 hours of receiving the information.

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

Response: Study personnel will make note of any health issues they observe or that the subject mentions spontaneously. Recording will include expected or unexpected Adverse Events such as illnesses, injuries, accidents, reactions to a concomitant medication, or worsening of a progressive disease state. An evaluation of the subject's extra- and intra- oral tissues will also be conducted to determine whether any visible adverse response to the test article occurred. In addition subjects will be queried about any other signs or symptoms they have noticed during the course of the study. Adverse events will be evaluated by the

Principal Investigator as to whether they were likely caused by the study mouthrinse and classified on the Adverse Events Form as related or unrelated to the study product. Adverse Events will also be classified as mild, moderate, or severe and reported by organ system.

21.3 Describe any safety endpoints.

Response: Adverse oral mucosal reactions.

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

Response: Adverse events will be evaluated by the Principal Investigator as to whether they were likely caused by the study mouthrinse and classified on the Adverse Events Form as related or unrelated to the study product. Adverse Events will also be classified as mild, moderate, or severe and reported by organ system

21.5 Describe the frequency of safety data collection.

Response: At each study visit, the subject will be asked an open-ended question about whether he/she experienced any changes in general health or medication intake since the prior visit; the response will be recorded.

21.6 Describe who will review the safety data.

Response: PI

21.7 Describe the frequency or periodicity of review of cumulative safety data.

Response: At each study visit, the subject will be asked an open-ended question about whether he/she experienced any changes in general health or medication intake since the prior visit; the response will be recorded.

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

Response: Safety will be assessed by subjective comments and oral hard and soft tissue exams. A comparison between test and placebo groups using a ***t test*** will allow us to compare any adverse effects occurring in the study.

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

Response: No adverse reactions resulting in suspension of the research is anticipated. The products being tested are commercially available and have a 510(K) approval by FDA. However, if an adverse event occurs that the PI determines to (1) have a serious effect on the health and well-being of the subject

and/or (2) be treatment-related, the study will be suspended immediately and reported to the IRB as soon as possible. If the adverse event is determined to be treatment related, the study will not be resumed. without the approval of the IRB.

22.0 Withdrawal of Subjects*

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

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

Response: Subjects enrolled in the study may elect to withdraw at any time for any reason. Additionally, subjects may be withdrawn from the study at the request of the Principal Investigator for the following reasons:

1. Subject does not return for follow-up and cannot be contacted to reschedule within +/- 5 days of each visit.

2. An adverse event that requires discontinuation of the study mouthrinse in the judgment of the Principal Investigator

3. Subject refusal or failure to comply with the study protocol

4. Protocol violation(s) or deviation(s) that compromise the use of the subject's data

5. Subject has started taking any concomitant medications that interfere with results including anticoagulants, NSAIDS, or drugs that have been shown to enlarge gingival tissues.

22.2 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: All subjects withdrawn from the study by request or by the Principal Investigator must be seen, if they consent, for a close-out evaluation. The reason for withdrawal will be recorded by the Principal Investigator or designee. Subjects who experience complications and discontinue the study on their own will be scheduled, if they consent, for an immediate follow-up/close-out examination to determine whether an adverse event is present, and if so, the causation of the adverse event will be recorded. If treatment is needed for any adverse event causing withdrawal, the subject will be monitored until return to normal conditions. Every effort will be made to follow up with subjects who withdraw from the study. The unused product will be disposed

22.3 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: If patients withdraw or are withdrawn from the study, the reason for withdrawal will be retained and de-identified in the final report of the study. Subjects who withdraw prior to last visit will be replaced with another subject and given the same treatment. To maintain the double-blind, the treatment will be determined by a third party who provided the randomization codes.

23.0 Risks to Subjects*

23.1 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: Possible adverse effects include dislike for taste and allergy to ingredient(s). Subject should not be or become pregnant while on this research study. Since the ingredients are considered to be safe(GRAS) by the U.S. Food and Drug Administration and some are found in food, the risk of a bad reaction or effect is low. Increase in plaque is not anticipated since the subjects will be allowed to brush in the study using their usual brushing method. Patient's proper oral hygiene regimen should control any significant plaque accumulation.

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

Response: Subjects who experience complications and discontinue the study on their own will be scheduled, if they consent, for an immediate follow-up/close-out examination to determine whether an adverse event is present, and if so, the causation of the adverse event will be recorded. If treatment is needed for any adverse event causing withdrawal, the subject will be monitored until return to normal conditions. (Every effort will be made to follow up with subjects who withdraw from the study.)

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

Response: Adverse effects to the mouthrinse.

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

Response: This study will not include pregnant women.

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

Response: We do not anticipate any risks to non-subject individuals.

24.0 Potential Benefits to Subjects*

24.1 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: There may be benefit to subjects. Possible benefits include additional moisturizing, lubrication and comfort to oral tissues.

25.0 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.

*25.1 **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: We do not anticipate research related injury. However, in the unlikely event of an adverse reaction, compensation will be carried out as follows: The subject will get medical treatment if injured as a result of taking part in this study. The study doctor will explain the treatment options to the subject and tell the subject where to get treatment. UB has no program to pay for medical care for research related injury. Generally, this care will be billed to the subject's insurance company or other third party.

25.2 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: The contract states similar information to that listed in 25.1 as follows: If a Study participant is injured from the investigational medical device or a study procedure that is required solely for Study purposes, Sponsor will be responsible to cover the cost of treating that injury (including hospitalization). Full financial responsibility for payment of such expenses resulting from an injury or illness suffered in the course of the Study will rest with the Sponsor, except to the extent that such expenses are attributable to the negligence or willful misconduct of the

Institution. In no event will Sponsor admit fault or liability on behalf of Institution without first obtaining Institution's prior written consent.

26.0 Economic Burden to Subjects

26.1 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 significant economic burden to the subjects due to enrollment in this clinical research. If the subjects do not have funds for travel to the study site, appropriate funds will be provided and deducted from their final compensation of $175.

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

27.0 Compensation for Participation

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

Response: Study subjects will be compensated $175 upon completion of the study. The study requires subjects to come to a clinic for a screening visit and 6 repeat visits and a payment of $175 check will partly compensate subjects for their mileage, time, and the inconvenience and slight discomfort of undergoing the dental examinations. Subjects will receive a check in the mail, 3-4 weeks after the completion of the study. There will be no compensation for the screening visit. If a subject voluntarily withdraws from the study, or if withdrawn by the Investigator for any reason, he/she will be compensated on a pro rata basis of $25 per completed visit with the exception of the screening visit.

☐ **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.

28.0 Consent Process

28.1 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)*

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

Response: At the screening visit prior to initiation of any study-related procedures, subjects will be informed about the nature and purpose of the study, the study procedures, participation and termination conditions, and the risks and benefits of participating. The subject will have the opportunity to ask questions about the study in private and then must freely agree to give written consent in order to participate in the study

28.3 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 adequate time at the screening visit to read the consent form and ask any questions related to the study

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

Response: This study includes only 6 visits over an 8-weeks period if the screening visit is at the same time as visit 1. Otherwise there will be 7 visits. Subjects enrolled in the study may elect to withdraw at any time for any reason.

28.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." Pay particular attention to Sections 5.4-5.9. 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)

28.6 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: Non-English speaking individuals will be included only if adequate translation support can be obtained. We will include a copy of written informed consent to IRB in a translated format prior to enrolling a subject that requires translation.

28.7 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, how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study, and any process to ensure ongoing consent. 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: Study personnel are primarily English speakers. If a non-English speaker would like to be enrolled in the study, they will be enrolled if translation support can be obtained for both oral and written communication in that language. The informed consent will be translated into the required language for the subject and explained by the translator, who will be present during all visits. The subject will be provided opportunity to ask questions to the study staff (through the translator) and make an informed decision.

Cognitively Impaired Adults

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

28.8 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).*

28.9 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)."

28.10 ***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: N/A.

28.11 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

28.12 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)*

*28.13 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: Subjects will be asked to provide a state-issued photo ID for confirmation of age.

*28.14**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

28.15 Describe whether parental permission will be obtained from:

Response:

☐ 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)."

*28.16 Describe 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

*28.17 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

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

Response: N/A

29.0 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.

29.1 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

29.2 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

30.0 Process to Document Consent

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

30.1 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: At the first visit prior to initiation of any study-related procedures, subjects will be informed about the nature and purpose of the study, the study procedures, participation and termination conditions, and the risks and benefits of participating. The subject will have the opportunity to ask questions about the study in private and then must freely agree to give written consent in order to participate in the study. HRP-502 is attached in the online IRB submission.

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

31.0 Multi-Site Research (Multisite/Multicenter Only)*

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

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

Response: N/A.

*31.2 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as the following. See "WORKSHEET: Communication and Responsibilities (HRP-830).":*

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

Response: N/A.

31.3 Describe the method for communicating to engaged participating sites (see "WORKSHEET: Communication and Responsibilities (HRP-830)"):

- *Problems (inclusive of reportable events)*
- *Interim results*
- *Study closure*

Response: N/A

31.4 If this is a multicenter study ***where you are a participating site/investigator****, describe the local procedures for maintenance of confidentiality. (See "WORKSHEET: Communication and Responsibilities (HRP-830).")*

- *Where and how data or specimens will be stored locally?*
- *How long the data or specimens will be stored locally?*
- *Who will have access to the data or specimens locally?*
- *Who is responsible for receipt or transmission of the data or specimens locally?*
- *How data and specimens will be transported locally?*

Response: N/A

31.5 If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described elsewheres in the protocol.

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

- *Describe the methods that will be used to identify potential subjects.*
- *Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)*

Response: N/A

32.0 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.

*32.1 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: N/A.

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

Response: N/A.

32.3 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: N/A.