EIRB Protocol Template (Version 1.3)

1.0 General Information

***Please enter the full title of your protocol:**

Can SAP P11-4 Increase The Radiopacity of Incipient Interproximal Carious Lesions on a Radiograph in a Military Population

***Please enter the Protocol Number you would like to use to reference the protocol:**

SAPP114
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site protocol (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add sites

2.1 List sites associated with this study:

Is Primary?	Site Name
◉	**P and R** - Tripler Army Medical Center (TAMC)

3.0 ■ Assign project personnel access to the project

3.1 * Please add a Principal Investigator for the study:

Name	Role	Training Record
Phung, Steven Minh	**Principal Investigator**	**View Training Record**

Responsibility

☐ Student
☐ Resident
☐ Site Chair
☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Name	Role	Training Record

No Additional Investigators have been added

B) Research Support Staff

Name	Role	Training Record
No Research Support Staff have been added		

3.3 *Please add a Protocol Contact:

Name	Role	Training Record
Phung, Steven Minh	**Study Contact**	**View Training Record**

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Name	Role	Training Record
No Designated Department Approval have been added		

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 * Is this protocol in support of a Graduate Health Science or other Allied Health Education Program?

(•) Yes ( ) No

If yes, check all that apply.

- [ ] Graduate Medical Education (GME)
- [x] Graduate Dental Education (GDE)
- [ ] Graduate Nurse Education (GNE)
- [ ] Graduate Allied Health Science
- [ ] Fellowship
- [ ] Other Allied Health Education Program

4.2 * What department(s) will be associated with this protocol?

	Dental Care

4.3 * Is the IRB of record for this study an IRB/HRPP that does NOT use EIRB? If Yes, complete the application according to the IRB /HRPP Determination.

If your Projects or Protocols are under the oversight of another IRB that does use EIRB, stop this submission and contact the core site and request an invitation as a performing site.

If your Project or Protocol is now being submitted for the first time to an IRB that does use EIRB, continue with this application and answer the questions to be reviewed by the IRB.

Answering yes means the board of record is an IRB that does NOT use EIRB.

○ Yes ◉ No

4.4 * Is this protocol research, expanded access, or humanitarian use device?

◉ Yes ○ No

4.5 * What type of protocol is this?

- ☐ Behavioral Research
- ☑ Biomedical Research
- ☐ Clinical trial (FDA regulated)
- ☐ Educational Research
- ☐ Expanded Access
- ☐ Humanitarian Use Device (HUD)
- ☐ Psychosocial Research
- ☐ Oral History
- ☐ Other

4.6 Are you conducting this project in pursuit of a personal degree?

○ Yes ◉ No

4.8 * Is this human subjects research? (As defined by 32 CFR 219) Human subject means a living individual about whom an investigator (whether professional or student) conducting research:
(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.

◉ Yes ○ No

4.9 * Do you believe this human subjects research is exempt from IRB review?

○ Yes ◉ No

5.0 Personnel Details

5.1 Does the Principal Investigator have a Permanent Change of Station (PCS) Date or Estimated Institutional Departure Date (EIDD)?

◉ Yes ○ No

Principal Investigator

Steven Minh Phung

06/15/2027

5.2 List any Research Team members without EIRB access that are not previously entered in the protocol:

Name: (Last, First, M.I.)		Email Address:	Associated Institution:

Belknap, William Role on Protocol: Associate Investigator	Phone Number: (808) 433-8945	William.j. belknap8. mil@health.mil	USUHS GDE, Schofield Barracks AEGD

5.3 Are any Contractors or Subcontractors involved in this study? If yes, please list them and describe their role.

○ Yes ◉ No

No results found

5.4 Will you have a Research Monitor for this study?

○ Yes
◉ No
○ N/A

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Is this study funded?

○ Yes ○ No

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

All personnel engaged in research must complete and attach a Conflict of Interest (COI) form.

8.0 Study Locations

8.1 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

○ Yes ◉ No

8.2 Study Facilities and Locations:

Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site
No results found						

Other:

Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site
No results found					

8.3 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

8.4 Is this an OCONUS (Outside Continental United States) study?

◉ Yes ○ No

Is this protocol conducted outside a DoD facility and/or including non-DoD affiliated personnel /beneficiaries (i.e. local foreign nationals)?

○ Yes ◉ No

9.0 Study Details

9.1 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

Remineralization, peptide, non-invasive, caries

9.2 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Dental caries, or cavities, is the most prevalent non-communicable disease in the world[5]. It has been shown that a majority of interproximal carious lesions, cavities that develop on the surfaces between neighboring teeth, are not cavitated[4] (i.e. they don't have holes yet and therefore have intact surfaces). These caries with intact surfaces are potentially good candidates for remineralization therapy[2] instead of irreversible, restorative treatment. Before irreversible, restorative treatment is performed, the dentist should consider the multitude of remineralization therapy options. Remineralization should be considered as first line therapy to reverse dental caries before cavities form, essentially preserving natural tooth structure. This may reduce long term cost and restorative needs for patients[2].

The aim of this study is to identify a new minimally invasive treatment option that can increase radiopacity of incipient interproximal caries in a military population. One such therapy is self-assembling peptide (SAP) P_{11-4}. This synthetic peptide forms a 3-dimensional matrix (a

biomimetic scaffold) within the body of an initial carious lesion by binding to calcium and phosphorous ions from the saliva which promotes the formation of hydroxyapatite crystals within the tooth[7]. An earlier version of Curodont was introduced in 2016 and Curodont Repair Fluoride Plus was available in 2019[7]. Curodont is available in nearly 12% of U.S. dental offices and has been used to treat over 2 million teeth[8]. On the other hand, the prevalence of Curodont in the military is unknown.

There is no one single or mandated standard of care for the treatment of early, non-cavitated interproximal carious lesions. However, a multitude of treatment option exist such as fluoride varnish, silver diamine fluoride, CPP-ACP paste (MI Paste), prescription strength fluoride toothpastes, fluoride mouth rinses, "watch and wait", or restorative treatment like a filling. A dentist takes into account numerous factors to determine the treatment modality that would best suit the patient and their condition. These factors could be caries risk, lesion activity (active or arrested), salivary flow, compliance with treatment, manual dexterity of the patient, patient autonomy, time constraints (PCS, ETS, TDY), and if the patient will be deploying to an area with limited access to care.

Military members are required to have a dental exam roughly every 12 months. It is likely that a patient may see a different dentist at every exam. A patient may have incipient interproximal carious lesions that are being treated with remineralization. Because the results of conventional remineralization therapy, like fluoride varnish, is not evident on a radiograph, the next provider may plan restorations for those incipient caries based on their radiographic appearance. With Curodont Repair Fluoride Plus, patients may have radiographic improvement of their interproximal lesions in addition to the remineralization effect of the product.

Curodont is currently not utilized as a treatment option at Schofield Barracks Dental Clinic. Its use in the military health system is unknown. It is also not currently listed in Defense Medical Logistics Standard Support (DMLSS) which is the military's software to track and order medical supplies. Typically, patients with incipient interproximal carious lesions indicated for Curodont would receive either of the following treatments: fluoride varnish at their annual teeth cleaning, "watch and wait", or no treatment.

Curodont Repair Fluoride Plus is indicated for early, non-cavitated carious lesions[8]. This could appear as white spots on buccal, lingual, or occlusal surfaces[8]. Interproximally, these lesions could be detected on radiographs. Lesions that penetrate up to the outer 1/3 of dentin may be treated with Curodont as long as they are not cavitated[8].

In a 2022 systematic review and meta-analysis of clinical trials involving SAP $P_{11-4,}$ the authors confirmed the absense of adverse events across 4 included studies, two of which explicitly looked for adverse events[6]. The material is characterized as biocompatible and non-toxic, posing minimal risk to both adult and pediatric patients[6].

This study will shed light on a current, minimally invasive treatment option, such as SAP P11-4, in a military setting. Minimally invasive treatment like Curodont Repair Fluoride Plus, could prolong the life of the tooth, lower long term health costs, and educate patients and providers on the importance of prevention.

9.3 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions /hypotheses

The aim of this study is to explore a non-invasive treatment option, Curodont Repair Fluoride Plus, that can increase radiopacity of incipient interproximal caries in addition to remineralizing those incipient interproximal caries in a military population.

9.4 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled,

cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

This will be an observational, case-series study design. A single intervention will be introduced, the results will be observed, and there will be no control group or control of other factors. The patient will be informed of alternative treatment options verbally. Alternative treatment options will also be included in the informed consent.

9.5 Target Population:

Describe the population to whom the study findings will be generalized

Active Duty servicemembers with incipient caries will be the population to whom the findings will be generalized.

9.6 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

Non-invasive treatment of incipient carious lesions can be a more cost efficient treatment than conventional fillings. Non-invasive treatment can take 3 minutes to apply, while filling appointments can take 45 minutes or more. Readiness and Wellness can be improved and maintained in a more quick and non-invasive way with the use of non-invasive treatment options. Additionally the cost of materials to provide non-invasive treatment is cheaper than the materials needed to provide a filling.

Expanding the use of non-invasive treatment options could prevent cavities from progressing to dental readiness class 3 emergencies that could restrict a Soldier's deployability.

Preserving the health of the Soldier's natural dentition can reduce the long-term need for more complex and costly prosthodontic or endodontic interventions later in their career.

The "no drill and no needles" aspect of remineralization therapy can potentially be effective in forward-deployed environments where traditional dental equipment and a handpiece may not be available.

10.0 Study Procedures, Data Management, and Privacy

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

Protocol for Research

1. Potential subjects who have at least one interproximal incipient lesion on bitewing radiograph that is E1 (halfway into enamel), E2 (more than halfway into enamel), or D1 (into the outer third of dentin) will be identified through referral from dental providers at the Schofield Barracks Dental Clinic (SBDC). Subjects must have non-cavitated lesions (verified clinically where possible or by the absence of a visible break in the enamel surface on the radiograph).
2. Patients will be contacted by the principal investigator (PI) after a referral is made from a referring dentist. The PI will schedule the subject's initial consent appointment.
3. The PI reviews the informed consent with the patient and gives patient the chance to ask questions
4. Signed consent will be obtained and the subject will be provided a copy of the signed form.
5. At the baseline study visit, a baseline bitewing will first be taken. The sensor will be centered on the interproximal lesion(s) that is being treated.
6. Curodont Repair Fluoride Plus will then be applied to the lesion(s) per the manufacturer’s instructions
7. At this visit, the PI will review with the patient a thorough OHI demo of proper brushing and flossing technique, reinforcing frequency and technique.

8. The patient will be scheduled to return at approximately 1 week, 1 month, and 3 months to obtain follow up bitewing radiographs of the treated lesion. The PI verbally reinforces OHI technique and frequency.
9. Images will be set with "No Real-Time Filter". Images will not be exported with enhancements or filters. Images will also not be exported with any identifiers.
10. Image processing software will be utilized to assess the radiographic effects of treatment
11. The ROI (Region of Interest) will be defined by using a standardized rectangular box to not include sound enamel, the outer enamel surface, or the dentinoenamel junction. The ROI defined at Baseline will be saved in the image processing software and overlaid onto subsequent recall radiographs aligned via anatomical landmarks to ensure the exact same pixel area is measured
12. Each subject will be assigned a unique subject ID to separate PHI from the study data. The Master Linking Log will be used to code the study data and will contain the unique subject ID, subject's name, DOB, DOD ID, phone number, and enrollment date. The Master Linking Log will be password protected and stored on a DOD network. The coded data collection sheet will be maintained separately from the Master Linking Log and also stored with a password, on the DOD network, with access limited to study team members. The radiographs will be exported from the X-ray software in the SBDC clinic and stored on a CAC-enabled government computer on the DOD network with limited access to just the study team.
13. The PI utilizes the "Relative Density" Formula: Relative Density = Mean Gray Value of the Lesion / Mean Gray Value of Sound Enamel. Sound Enamel will be defined as a radiopaque area on the enamel of the same tooth at least 2mm away from the interproximal carious lesion that is being treated. The area selected as Sound Enamel defined at baseline will be overlaid onto subsequent recall radiographs aligned via anatomical landmarks to ensure the exact same pixel area is measured. Result = 1.0: The lesion is as dense as healthy tooth. Result < 1.0: The lesion is less dense.
14. The PI will compare the Mean Relative Density at Baseline vs. 1 week, 1 month, and 3 month utilizing One-Way Repeated Measures ANOVA. All statistical tests will be two-tailed with a significance level set at $\alpha = 0.05$.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, and how the data will be operationally measured.

Data will consist of bitewing radiographs extracted from the X-ray software. PHI consisting of the subject's name, DOB, DOD ID, phone number, and enrollment date will be recorded in the Master Linking Log.

10.3 At any point in the study, will you request, use, or access health information in any form, including verbal, hard copy and electronic?

(•) Yes ( ) No

10.4 Review the definitions below and respond to the following two questions. If you are not sure of the answers, email DHA. PrivacyBoard@mail.mil for assistance. The *Military Health System (MHS)* is defined as all DoD health plans and DoD health care providers that are organized under the management authority of, or in the case of covered individual providers, assigned to or employed by, the Defense Health Agency (DHA), the Army, the Navy, or the Air Force *MHS workforce members* are employees, volunteers, trainees, and other persons whose conduct, in the performance of work for the MHS, is under the direct control of the MHS, whether or not they are paid by the MHS. *MHS business associates* are persons or entities that provide a service to the MHS and require protected health information (PHI) to provide the service.

Are you an MHS workforce member?

(•) Yes, I am an MHS workforce member
( ) No, I am not an MHS workforce member

10.5 Have you consulted with an MHS data expert to determine the data elements required for your study?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**DHA.PrivacyBoard@mail.mil**)

- ○ Yes, then complete the questions below according to the data consult
- ◉ No, then complete the questions below according to the best of your knowledge

10.6 Indicate how you will request data from the MHS. Select all that apply.

- ☐ Talking with MHS health care providers or MHS health plans about specific research participants
- ☐ Obtaining MHS hard copy records specific to research participants
- ☑ Obtaining data from an MHS information system(s)

10.7 If you are obtaining data from an MHS information system(s), indicate whether you plan to receive a data extract or whether you plan to access an MHS information system directly to create a data set.

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

- ☑ Data Extract
- ☑ Access

10.8 Do you intend to request de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

- ○ Yes ◉ No

10.9 Indicate the MHS information system(s) from which you will seek to obtain data

If you do not know which system(s) contains the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or request guidance from an MHS data expert at: **DHA.PrivacyBoard@mail.mil**.

Below is a list of commonly used MHS systems. If the system from which you seek to obtain data is not listed below, list the name of the system in the "Other MHS Systems" category below
PHI Systems:

MHS Information System	Requesting Data
: MHS Genesis	: Yes

PII-Only Systems:

MHS Information System	Requesting Data
No results found	

De-Identified Data & Other Systems:

Information System	Requesting Data
Other MHS System May include PII and/or PHI List other system here: XrayVision DCV	: Yes

10.10 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- ○ Yes, will merge data
- ◉ No, will not merge data

10.11 Indicate the data elements about research participants or relatives, employers, or household members of the research participants that you will request from MHS hard copies or from MHS information systems.
If you will merge data, also indicate non-MHS data elements about research participants or relatives, employers, or household members of the research participants that you will have access to in any form or medium.

Direct and Indirect Identifiable Data Elements	DHA Hard Copies	DHA Data Elements to be Accessed	DHA Data Elements Verbal	Extracted DHA Digital Data	Downloaded DHA Digital Data	Non-DHA Hard Copies or Digital
1. Names	☐	☑	☐	☐	☐	☐
2. Postal address with only town, city, state, and zip code	☐	☐	☐	☐	☐	☐
3. Postal address with all geographic subdivisions smaller than state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by	☐	☐	☐	☐	☐	☐

combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code from all such geographic units containing 20,000 or fewer people is changed to 000						
4. Dates including all elements (except year) directly related to an individual, including birthdate, admission date, discharge date, and date of death	☐	☑	☐	☐	☐	☐
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"	☐	☐	☐	☐	☐	☐
6. Telephone Numbers	☐	☑	☐	☐	☐	☐
7. Fax Numbers	☐	☐	☐	☐	☐	☐
8. Email Addresses	☐	☐	☐	☐	☐	☐

9. Social Security Numbers	☐	☐	☐	☐	☐	☐
10. Medical Record Numbers (MRN) (including record ID)	☐	☐	☐	☐	☐	☐
11. Health Plan Beneficiary Numbers (including DEERS ID, Electronic Data Interchange Personal Identifier (EDIPI) or Number (EDIPN))	☐	☑	☐	☐	☐	☐
12. Account Numbers	☐	☐	☐	☐	☐	☐
13. Certificate /License Numbers	☐	☐	☐	☐	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐	☐	☐	☐	☐
15. Device identifiers and serial numbers	☐	☐	☐	☐	☐	☐
16. Web Universal Resource Locators (URLs)	☐	☐	☐	☐	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐	☐	☐	☐	☐

18. Biometric identifiers, including finger and voice prints	☐	☐	☐	☐	☐	☐
19. Full-face photographic images and any comparable images	☐	☐	☐	☐	☐	☐
20. Any other unique identifying number, characteristic, or code (including non-military provider IDs)	☐	☐	☐	☐	☐	☐
21. Free Text Fields	☐	☐	☐	☐	☐	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used.

Due to guidelines stated within DoDI 1000.30, Reduction of SSN Use within DoD, the reduction or elimination of SSN usage must occur wherever possible. If SSNs are required to complete the project, the PI must provide a justification and explanation as to why a substitution cannot be used.
For example:

- If alternatives to SSN (e.g., EDIPNs or pseudo person IDs) are sufficient in other instances, will those alternatives to SSN usage be sufficient to respond to Congressional inquiries and /or Senior DoD stakeholders inquiries?
- Are alternatives to SSN used first?
- Are those alternatives to SSN insufficient to combine data from multiple data sources? Is the issue that some individuals do not possess alternatives ID numbers and SSN is the only way to identify them?

a. Will you receive or obtain health information?

> ***Note:*** *If you indicate you are not receiving health information, the answer must be consistent with the DHA data source. For a non-health information data request, if you are a non-MHS employee or non-MHS business associate, you may not access an information system that has PHI or LDS. For both MHS and Non-MHS employees and MHS business associates, you may* ***NOT*** *include data elements in the above table on: 1) lines 10 or 11, 2) line 21 if the free text field comes from a PHI or LDS system, and 3) lines 12, 13, or 18 if the account numbers, certificate and license numbers, biometric data, or any other data elements are health*

information created or received by an MHS health care provider, health plan, or business associate in relation to the physical or mental health or condition of an individual or payment for health care.

- (•) Yes, I will receive or obtain health information
- ( ) No, I will not receive or obtain health information

b. If no data elements were checked in the above table, is it possible that the requested DHA data is or will be identifiable because of any unique data elements, triangulation, or small cell size?

- [x] Data elements were checked in the above table, STOP HERE.

NOTE: *A unique data element includes any unique features that alone are not identifiable but that could be used to identify an individual within the context of other information, such as any type of code (such as diagnosis or procedural), rank of general or admiral, sex, or race. Triangulation means using different data elements that when combined can be used to identify an individual, such as including the above lists of unique data elements in a data set. Determining whether an individual is identifiable through triangulation requires consideration of all data elements in combination. Within the military, the use of rank and/or diagnosis code, procedural codes, or any other code that changes on a predictable basis, increases the possibility of identification. Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Department of Defense Manual 6025.13, Medical Quality Assurance and Clinical Quality Management in the Military Health System MHS, provides that the threshold for de-identifying data within the MHS requires a cell size of three, but also states that the de-identification standards must meet the DoD implementation of the HIPAA Privacy Rule. Centers for Medicare and Medicaid also gives guidance on small cell size stating that no data cell less than 11 may be published or displayed. However, the Office for Civil Rights' OCR, which is the official regulatory office for the HIPAA Privacy Rule, provides that OCR does not designate a universal value for small cell size in accordance with the de-identification standard; instead, the cell size should be set at a level that is appropriate to mitigate risk of identification by the anticipated recipient of the data set. This means that a cell size of 3 or 11 may not meet the HIPAA Privacy Rule requirements if the cell size level does not appropriately mitigate risk of identification by the anticipated recipient of the data set.*

Note: If dates are altered as a means of de-identifying the data, diagnosis and procedural codes need to be rolled-up or collapsed. If dates are provided "as time between events," the roll-up is not necessary.

- [ ] Yes, the DHA data will become identifiable
- [ ] No, the DHA data will not become identifiable

10.12 Do you believe it is possible for the MHS data to become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would use rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30, so the rank category may need to be expanded to include lower ranks.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 20 of the table above (in Section 10.10), but that could be used to identify an individual. Unique data elements include characteristics that are not themselves identifying, such as the rank of general or admiral, or a race or sex, but within the context of other information could be identifiable.

- ( ) Yes, I believe there is a reasonable possibility the MHS data will become identifiable
- (•) No, I believe there is no reasonable possibility the MHS data will become identifiable

10.13 Have you completed and uploaded an appropriate HIPAA document (i.e. HIPAA Authorization will be obtained or Waiver/alteration of HIPAA Authorization is being requested)?

- (•) Yes
- ( ) No
- ( ) N/A

If yes, please check which one.

- [x] HIPAA Authorization
- [x] HIPAA Waiver (Full or Partial)
- [ ] Other (please provide copies when uploading Other Study Documents)

10.14 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

The data collection sheets (Master linking log and coded data collection sheets) will be password protected and stored on a password protected laptop on the DOD Network on the principal investigator's personal government OneDrive. Only the study team will have access to the drive and documents. A Master Linking Log will be utilized to secure patient identities during data collection and to guard against beach of confidentiality. The Master Linking Log will be kept separately from all other study documents and and will be destroyed when the study has been completed. Radiographs will be exported from XrayVision with no patient information in the file name or in the image that will be exported. Radiographs will be linked to the unique subject ID. After the study has been completed, data will be stored for at least 6 years. This will include HIPAA authorizations, consent forms, data forms that record the measured gray values, IRB Approval Letter, and adverse event logs. Data will not be shared with any team member outside of Tripler Army Medical Center.

Paper documentation and consent forms will be stored in the associate investigator's office in a lockable filing cabinet. After each patient, consent forms will be secured at the PI's filing cabinet. Then, at the end of each day after the last study patient, paper forms will be compiled and stored in the associate investigator's office. The study team member's office and the cabinet will be locked at the end of each day. Per TAMC policy, study documents will be retained for at least 6 years.

Is this a data repository?

( ) Yes (•) No

10.15 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens/data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed.

Data from this study will not be utilized for future research.

Is this a data repository?

( ) Yes (•) No

11.0 Statistical/Data Analysis Plan

11.1 Data Analysis Plan and Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any subgroup analyses (e.g., sex or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis.

The depth of the Region of Interest will be defined as either E1, E2, or D1 depending on the deepest extent of the caries as it appears on bitewing radiographs. As interproximal caries typically appear triangular in shape with the base on the outer surface of the enamel and the apex of the triangle pointing towards the center of the tooth, the apex of the triangular shape will be utilized to determine the depth of the ROI. The area selected as the ROI will be a standardized rectangular box approximately centered within the lesion that will not include areas of sound enamel, the outermost edge of enamel, or the dento-enamel junction, all of which may obscure gray values.

The principle investigator utilizes the "Relative Density" Formula: Relative Density = Mean Gray Value of the Lesion / Mean Gray Value of Sound Enamel. Sound Enamel will be defined as a radiopaque area on the enamel of the same tooth at least 2mm away from the interproximal carious lesion that is being treated. The area selected as Sound Enamel defined at baseline will be saved in the ImageJ ROI Manager and overlaid onto subsequent recall radiographs aligned via anatomical landmarks to ensure the exact same pixel area is measured. Result = 1.0: The lesion is as dense as healthy tooth. Result < 1.0: The lesion is less dense.

The principle investigator will compare the Mean Relative Density at Baseline vs. 1 week, 1 month, and 3 month utilizing One-Way Repeated Measures ANOVA. All statistical tests will be two-tailed with a significance level set at $\alpha = 0.05$.

There are a couple of confounding variables to acknowledge in this study.

- a change in the angulation of the x-ray tube can change the appearance of lesions on a radiograph. This will be mitigated by utilizing a standardized x-ray sensor holder (red bitewing XCP), obtaining open contacts (proper angulation where there is no overlap of adjacent teeth), and centering the sensor on the lesion to be treated.
- there may be differences in the levels of fluoride that patients are exposed to in this study through oral care products that are used, the fluoride in community water, and dietary sources of fluoride. This will be mitigated through standardizing the oral hygiene instruction that is given to the patient at their initial appointment.
- there may also be differences in patients' diets that could affect results. Differences in diets or consumption of sugary foods/beverages could affect the extent of remineralization. This will be mitigated through standardizing the nutritional counseling that is given to the patients as part of their oral hygiene instruction.
- differences in salivary flow could affect results. Patients may have varying levels of salivary flow or be taking medications that affect salivary flow. We acknowledge that this may be a confounding variable.

11.2 Sample Size:

30

11.3 Total number of subjects requested (including records and specimens):

30

11.4 Are you recruiting participants by study arm?

○ Yes ○ No

11.5 Please provide a justification for your sample size

An a priori power analysis was conducted to determine the required sample size. Based on a One-Way Repeated Measures ANOVA with 4 measurements, a significance level of alpha = 0.05, a

power of 0.80, and assuming a large effect size (d=0.8), a minimum of 15 subjects is required. To account for an expected 20% attrition rate over the 3-month follow-up period, a total of 20 subjects will be enrolled. Reconsidering that susceptibilities for dental caries varies for different sex and age groups, increasing the sample size beyond 20 will help ensure the study findings are clinically relevant across the target demographic. A larger sample size will prevent the study from being limited to a generalized conclusion that may hide significant variation in treatment efficacy between age groups.

12.0 Participant Information

12.1 Subject Population:

Active duty patients that have at least 1 or more incipient, non-cavitated, interproximal carious lesions (E1, E2, or D1) who have at least 4 months remaining on station from the start of the research project.

12.2 Age Range:

Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

- [ ] 0-17
- [x] 18-24
- [x] 25-34
- [x] 35-44
- [x] 45-54
- [x] 55-64
- [x] 65-74
- [ ] 75+

12.3 Sex:

- [x] Male
- [x] Female
- [ ] Unknown

12.4 Special categories, check all that apply

- [ ] Minors /Children
- [ ] Students
- [ ] Employees - Civilian
- [ ] Employees - Contractor
- [ ] Resident/trainee
- [ ] Cadets /Midshipmen
- [ ] Active Duty Military Personnel
- [ ] Wounded Warriors
- [ ] Economically Disadvantaged Persons
- [ ] Educationally Disadvantaged Persons
- [ ] Physically Challenged (Physical challenges include visual and/or auditory impairment)
- [ ] Persons with Impaired Decisional Capacity
- [ ] Prisoners
- [x] Pregnant Women, Fetuses, and Neonates
- [ ] Non-English Speakers
- [ ] International Research involving Foreign Nationals - Headquarters Review is necessary

12.5 Inclusion Criteria:

Order Number	Criteria
1	Active duty military
2	must have 1 or more incipient, non-cavitated, interproximal carious lesions (E1, E2, or D1 in radiographic depth)
3	must have time remaining on post for at least 4 months from start of treatment

12.6 Exclusion Criteria:

Order Number	Criteria
1	Non-active duty military
2	interproximal carious lesions that are cavitated or D2-D3 in radiographic depth
3	tobacco, nicotine, and e-cigarette users

13.0 Recruitment and Consent

13.1 Will subjects be identified and selected for study participation?

(•) Yes ( ) No

If yes, please describe the recruitment process, including how subjects will be identified and selected for the study

Under an approved Partial HIPAA Waiver Application for this study, the study team members will review medical records of Schofield Barracks Dental Clinic patients for incipient carious lesions in order to identify prospective research participants to approach and offer them the opportunity to participate in this research study

CPT Steven Phung will identify potential subjects by evaluating his own patients at Schofield Barracks Dental Clinic for incipient carious lesions as part of their comprehensive care. Patients will also be referred to CPT Phung from general dentists at Schofield Barracks Dental Clinic. Referring general dentists will give patients a flyer with CPT Phung's contact information.

13.2 Will subjects be compensated for study participation?

( ) Yes (•) No

13.3 Will pre-screening of subjects occur?

(•) Yes
( ) No
( ) N/A

If yes, please describe the pre-screening process

Patients will be screened by evaluating their bitewing radiographs as part of their comprehensive care. Participation in the study will require the presence of 1 or more incipient, interproximal, non-cavitated carious lesions that are E1, E2, or D1 in depth. Patients will also be required to be present for at least 4 months from the start of their treatment. Patients must be 18 years or older to participate. Patients must also be Active Duty. Patients who use tobacco products, nicotine products, or e-cigarettes will not be able to participate in this study.

13.4 Consent Process: Revised Common Rule, Section 219.116: General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens.

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

The first visit will be a 60 minute appointment where we go over the consent form and talk about what to expect for the study. It will take place in Schofield Barracks Dental Clinic in a private operatory with CPT Steven Phung and the patient. CPT Phung and the patient will go over the consent together and the patient will have the opportunity to ask questions. All questions will be answered to the patient's satisfaction prior to signing the consent form. Team members will wear civilian or hospital scrubs with no identifiers or name tags that include rank to avoid coercion.

13.5 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

◉ N/A
○ Propose ombudsman

13.6 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Patients that wish to withdraw from the study must let someone in the research team know. This can be communicated verbally or in writing.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

Researchers will make every effort to protect your privacy and confidentiality; however, there are risks of breach of information security and information loss.

The dental material to be tested in this project, Curodont Protect Fluoride Plus, has no reported side effects and no reported adverse events.

As part of this study, standard digital X-rays will be taken of your teeth. Radiation exposure from these digital X-rays is same as 1-2 days of naturally occurring background radiation or less than flying in a commercial flight from across the pacific ocean. Therefore, this amount is so small, the risk of any harm to your health is extremely low.

Risk Mitigation and Safety Measures: The radiation exposure from these dental X-rays is considered minimal. To ensure participant's safety and maintain exposures As Low As Reasonably Achievable (ALARA), your standard radiation safety practices should be followed i.e. lead aprons and thyroid collars are no longer recommended standard radiation protection.

14.2
Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

All data will be stored on a password protected computer on the government approved DOD network on a password protected document that has limited access to just the principal investigator.

A Master Linking Log will be utilized to separate subjects PHI from the study data. This Master Linking Log will be password protected and stored separately from all other study documents on a DOD network on the principal investigator's government drive and never printed

All dental materials will be utilized per the manufacturer's instructions.

14.3
Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e. g., child or spouse abuse

All data will be stored on a password protected computer on the government approved DOD network on a password protected document that has limited access to just the study team.

A Master Linking Log will link each subject to their study data using a unique subject ID. The Master Linking Log will be kept separately from all other study data on a password protected government computer on a DOD network, only accessible by the PI and never printed. This log will be destroyed upon completion of the study project.

Study documents to include consent forms, HIPAA authorizations, and data sheets recording grayscale values will be retained for at least 6 years.

Hard copy consent forms will be stored in the PI's filing cabinet after each patient. At the end of each day and after all study patients have been seen for the day, the hard copy consent forms will be stored in the associate investigator's office in a lockable filing cabinet. The associate investigator's office and the filing cabinet will be locked at the end of each day.

Name and DOB will be utilized to identify patients prior to seating them in the dental chair. DOD ID must be utilized in order to capture radiographs into x-ray software.

Recruitment and Intervention will take approximately 4-5 months. Data analysis and manuscript preparation will take approximately 2-3 months. Records will be retained for a period of 6 years per TAMC policy following formal close of the study.

After expiration of this retention period, all paper and electronic documents will be destroyed and wiped digitally. Additionally, all paper and electronic documents containing PII/PHI will be destroyed and wiped digitally after the 6 year retention period.

14.4
Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

Participation in this research study has several benefits to include remineralization and treatment of early decay/cavities before it becomes worse or deeper. Another benefit is that subjects would receive non-invasive treatment that does not involve drilling or needles. Subjects will also receive one-on-one oral hygiene instruction and demonstration from a licensed dentist.

The intended outcome of this study is the promote preventative dentistry in the Army and to educate soldiers on the various ways they can take part in their own oral health. As a potential result, soldiers could be spending less appointment time dealing with the consequences of decay and tooth loss.

The dental material to be tested in this project, Curodont Protect Fluoride Plus, has no reported side effects and no reported adverse events.

14.5
Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

During the recruitment process, dentists who refer potential study subjects to the principal investigator can communicate directly to the principal investigator verbally or in an encrypted government email message. During the consent process, the only personnel in the treatment operatory will be the patient and the principal investigator.

Encrypted emails will be sent only to the PI. Encrypted emails will only be accessible on the PI's CAC-enabled government computer on the PI's personal government approved DOD network. Once patients are enrolled into the study, their information will be input into a Master Linking Log and the encrypted email will be deleted. If patients referred through encrypted email are not enrolled into the study, the email will be deleted.

All data will be stored on a password protected computer on the government approved DOD network on a password protected document that has limited access to just the principal investigator.

A Master Linking Log will link each subject to their study data using a unique subject ID. The Master Linking Log will be kept separately from all other study data on a password protected government computer on a DOD network, only accessible by the PI and never printed. This log will be destroyed upon completion of the study project.

14.6
Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the

results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

The subjects will have several opportunities to meet directly with the principal investigator at their consent and treatment appointment, 1 week recall, 1 month recall, and 3 month recall appointments. At these visits, an incidental findings will be discussed with the patient. Any incidental findings requiring dental treatment will be updated in the patient's chart.

Complete confidentiality cannot be promised for military personnel, because information regarding your health may be required to be reported to appropriate medical or command authorities to ensure the proper execution of the military mission, including evaluation of fitness for duty.

15.0 Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).

- ○ DSMP
- ○ DSMB
- ○ Both
- ◉ Not Applicable

16.0 Reportable Events

16.1 Reportable Events: Consult with the research office at your institution to ensure requirements are met. Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event.

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

Adverse Events will be reported by the principal investigator to the TAMC HPD/HRPO as well as the IRB.

While the product to be used in the study has no reported side effects or adverse events, any unexpected sensitivities or allergic reactions will be documented as an adverse event. Management of sensitivities or allergic reactions will include weekly follow-up visits for 2 weeks. Serious adverse events are not anticipated, but will be reported to the IRB within 48 hours if they occur.

The principal investigator will identify adverse events through clinical examination at 1 week, 1 month, and 3 month follow-up visits. Subjects will also be prompted to report any localized sensitivity, gingival irritation, or allergic reaction experienced since the application of Curodont Repair Fluoride Plus. Any incident that is unexpected, related, or possibly related to the research, and suggests the research places subjects at a greater risk of harm than previously recognized will be classified as unanticipated problems.

The principal investigator and the adjunct/associate investigator will determine if the informed consent needs to be updated to include new risk information or if the research protocol requires modification.

To ensure standardization of reporting, the following three-point scale will be used to grade the severity of any Adverse Event:

- Grade 1 (Mild) - transient or mild discomfort; no medical intervention required; does not interfere with the subject's daily activities or oral function.
- Grade 2 (Moderate) - mild to moderate limitation in activity; some assistance or localized clinical treatment may be needed
- Grade 3 (Severe) - marked limitation in activity; requires significant medical or dental intervention; results in permanent change to the subject's health status

For a minimal risk study using a topical agent, most Adverse Events (if any) are expected to be Grade 1 (e.g. temporary taste perversion)

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs, dietary supplements, biologics, or devices be utilized in this study?

☑ Drugs
☐ Dietary Supplements
☐ Biologics
☐ Devices
☐ N/A

18.2 Drugs, Dietary Supplements and Biologics/Vaccines details:

☑ Are drug(s) in this research being used in accordance to the approved labeling?
☐ Are drug(s) in this research being used in a manner other than its approved labeling?

Enter Dietary Supplements and Biologics/Vaccines in the Drug Information table. Complete all relevant fields in the table ("Protocol Drug Details" screen). If the question is not relevant, leave the question blank and/or do not change the default selection.

View Details	Drug Name	FDA Approved	A new drug or a new use of an already approved drug:	IND Number
⊟	**Trade Drug Name:** Curodont Repair Fluoride Plus **Generic Drug Name:** **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	Curodont Repair Fluoride Plus
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	VVardis Professional Switzerland supplied through Henry Schein ordered via credit card order
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	The investigators determine that this research study is exempt from the requirements for IND application based on the following criteria: - Curodont Repair Fluoride Plus is marketed in the United States as an OTC anticavity drug product complying with the FDA OTC Monograph - the investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use, nor is it intended to be used to support any other significant change in the labeling of the drug. The data are being collected for academic purposes only. - as this is an investigator-initiated study, there is no intent to use the results to support a significant change in the advertising or commercial promotion of the product. - the investigation does not involve a change in the route of administration, dosage level, or patient population
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	
Frequency:	
Route of administration:	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	
Identify who will be preparing the investigational drug /biologic for administration and describe in detail how it will be prepared:	The principal investigator will be preparing Curodont Repair Fluoride Plus per the manufacturer's instructions. The PI will peel the cover off Unit A to expose the sponge. The PI will retrieve one unit of Unit B dropper. The PI will immerse the sponge fully with Unit B liquid and let it soak for at least 2 minutes.
Indication(s) under Investigation:	
Where will the drug be stored	The drug will be stored at room temperature in a dry, cool place in the principal investigator's office.
Drug Storage Restrictions (including temperature, etc.):	The drug will be stored at room temperature in a dry, cool place

Administration Instructions:	The PI will peel the cover off Unit A to expose the sponge. The PI will retrieve one unit of Unit B dropper. The PI will immerse the sponge fully with Unit B liquid and let it soak for at least 2 minutes. While the sponge is soaking, the PI will prepare the treatment site by using either pumice, prophy paste, or air polisher. The PI will rinse and dry, etch using 35% phosphoric acid for not more than 20 seconds, unwaxed dental floss will be utilized to apply the etchant to interproximal sites, rinse and dry, and once the sponge is fully saturated and soft, place the cotton rolls around the treatment site. The PI will pick up the soft saturated sponge with cotton pliers or hemostats, press it on or near the lesion for 5 seconds using one sponge per lesion. For interproximal application, the sponge will be applied from the lingual embrasure followed by the buccal embrasure. The patient will be instructed not to eat, drink, spit or rinse for 30 minutes after application. The sponge and dropper will be disposed.
Possible Untoward Effects, Their Symptoms & Treatment:	N/A
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	N/A
Contraindications and Interactions, If Known:	N/A
Investigators Authorized to Prescribe:	CPT Steven Phung, DMD LTC William Belknap, DDS

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

N/A. The investigators determine that this research study is exempt from the requirements for IND application based on the following criteria: - Curodont Repair Fluoride Plus is marketed in the United States as an OTC anticavity drug product complying with the FDA OTC Monograph - the investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use, nor is it intended to be used to support any other significant change in the labeling of the drug. The data are being collected for academic purposes only. - as this is an investigator-initiated study, there is no intent to use the results to support a significant change in the advertising or commercial promotion of the product. - the investigation does not involve a change in the route of administration, dosage level, or patient population

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

○ Registration is not required
◉ Registration pending
○ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

- ○ Registration is not required
- ◉ Registration pending
- ○ Registration complete

20.0 References and Glossary

20.1 References:

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2. Diefenderfer, K. E., & Stahl, J. (2008). Caries remineralization therapy: implications for dental readiness. Military medicine, 173(1 Suppl), 48–50. **https://doi.org/10.7205/milmed.173.supplement_1.48**

3. Mascarenhas, A. K. (2021). Is fluoride varnish safe? The Journal of the American Dental Association, 152(5), 364–368. **https://doi.org/10.1016/j.adaj.2021.01.013**

4. Pitts NB, Rimmer PA. An in vivo comparison of radiographic and directly assessed clinical caries status of posterior approximal surfaces in primary and permanent teeth. Caries Res. 1992; 26(2): 146-52.

5. Ruff, R. R., Barry Godín, T. J., & Niederman, R. (2024). Noninferiority of Silver Diamine Fluoride vs Sealants for Reducing Dental Caries Prevalence and Incidence: A Randomized Clinical Trial. JAMA pediatrics, 178(4), 354–361. **https://doi.org/10.1001/jamapediatrics.2023.6770**

6. Shaalan, O., Fawzy El-Sayed, K., & Abouauf, E. (2024). Evaluation of the remineralization potential of self-assembling peptide P11-4 with fluoride compared to fluoride varnish in the management of incipient carious lesions: a randomized controlled clinical trial. Clinical oral investigations, 28(8), 438. **https://doi.org/10.1007/s00784-024-05822-z**

7. vVardis Inc. (n.d.). vVardis professional US. **https://professional.vvardis**.us/

20.2 Abbreviations and Acronyms:

PI = principal investigator
SBDC = Schofield Barracks Dental Clinic
OHI = Oral hygiene instructions
SAP = self assembling peptide