Reducing Oral Health Disparities of Older Adults: Comparative Effectiveness of 2 Treatments

Contract #: AD-2018-C1-10590

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Version Revision History:

Version #	Version Date	Summary of Revisions Made:
0.1	28 March, 2019	Initial draft
1.0	23 April, 2019	IRB Approval
1.1	3 May, 2019	Section 13.2.1 Quality Assurance Procedures was updated. Section 15.2 Data Collection Methods and Organization of the Data was updated.
2.0	3 May, 2019	PCORI Methodology Standards were added
3.0	18 October, 2019	PCORI Program Officer information updated, Key Personnel updated (removed Dr. Pinto and added Dr. Dubaniewicz). Sections 7.1, 7.2, 7.3, 8.1.1, 9.2 and Figure 15.3.1 were updated to add the Safety Questionnaire (Pre-Exam).
4.0	28 October, 2019	Sections 6.2 and 6.10 were updated to indicate that a rotary brush will not be used for the ART treatment procedure, only a manual brush. Sections 6.10, 7.1 and 7.2 were updated to outline procedures for addressing participant reported issues with the applied treatment.
5.0	11 November 2019	Sections 4.1 and 5 have been revised to add severe cognitive impairment as an exclusion criteria at the recommendation of the study's Data and Safety Monitoring Board. Revisions have been made to section 5 to clearly outline the screening and enrollment process for the study.
6.0	3 April 2020	Section 7 (Study Schedule) has been revised to add temporary COVID-19 procedures for obtaining written informed consent and collecting survey data at baseline and 26-week follow-up.
7.0	17 June 2020	Section 7 (Study Schedule) has been revised to add temporary COVID-19 in-person procedures for recruitment, data collection and dental screening/treatment. Section 1 has been updated with the current name and contact information for the PCORI Program Official and Key Personnel.
8.0	10 August 2020	Section 7 (Study Schedule has been revised to include that study exams/treatment during temporary COVID-19 in-person visits may take place in an outside location at the facility if requested by housing site personnel.

9.0	9 October 2020	Section 7 (Study Schedule) has been revised to be consistent with current screening guidelines indicating that individuals with a self-reported or on-site screening temperature > 100.0, will not be scheduled nor seen for a study visit or exam/treatment. Previously, the cut-off temperature was 100.4. Section 7.2 and 7.3 have been revised to correct the window timeframes.
10.0	13 November 2020	Section 7 (Study Schedule) has been revised to include remote data collection for questionnaires at the 52-week follow-up visit rather than in-person during the COVID-19 pandemic. Section 7.3 has been updated to include administration of the COVID-19 dental visit questionnaire at the 52-week follow-up visit, and section 6.11 has been corrected to indicate the proper arms.
11.0	29 September 2021	Updates have been made to the PCORI program official name and contact information. The Protocol Summary and sections 4, 5, 7.3 and 8.1.2 have been updated to reflect PCORI approved modifications to the study timeline (+18 months), # to be enrolled (+40) and # of facilities (+4) to address COVID-19 challenges. Section 8.1.2 has also been updated to indicate that focus groups may be conducted at a housing site or virtually based on housing site circumstances at the time of scheduling.
12.0	16 June 2022	Section 1: Study Sites was updated to add Educator Senior Housing.
13.0	4 Oct 2022	Section 1: Study Sites was updated to add Lorain Square and Beachcrest.
14.0	11 April 2023	The Protocol Summary was updated to reflect the correct # of added sites. Section 1: Study Sites and Section 4.1: Facility Table were updated to add all sites where recruitment/enrollment was completed. Key Roles and Contact Info. was updated to add Gloria Bales as the Research Associate. Sections 6.8 and 6.11 were updated to reflect that the study dentist may not be present at 52 week follow-up visits where treatment is not delivered. Section 7.3 was updated to reflect that the dentist or hygienist will administer the Safety Questionnaire (pre-exam) at the 52-week follow-up visit.

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the PCORI Contract for funded research project. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name: Suchitra Nelson, PhD

Title: Assistant Dean of Clinical and Translational Research
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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ACA	Affordable Care Act
ADA	American Dental Association
ART	Atraumatic Restorative Treatment
CRF	Case Report Form
CWRU	Case Western Reserve University
CHAID	Chi-Squared Automatic Interaction Detection
CART	Classification And Regression Trees
CONSORT	Consolidated Standards Of Reporting Trials
DSMB	Data Safety And Monitoring Board
DHHS	Department of Health and Human Services
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
FV	Fluoride Varnish
GEE	Generalized Estimating Equations
GOHRQoL	Geriatric Oral Health Quality Of Life
GIC	Glass Ionomer Cement
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HUD	Housing And Urban Development
IRB	Institutional Review Board
ICDAS	International Caries Detection And Assessment System
ICMJE	International Committee of Medical Journal Editors
ICH	International Conference On Harmonisation
ICC	Intraclass Correlation
IDE	Investigational Device Exemption
IDE	Investigational Device Exemption
IND	Investigational New Drug
IND	Investigational New Drug Application
MCAR	Missing Completely At Random
NCOA	National Council On Aging
NHANES	National Health And Nutrition Examination Survey
NIH	National Institutes Of Health

NIH	National Institutes of Health
NDA	New Drug Application
PCORI	Patient-Centered Outcomes Research Institute
PROMIS	Patient-Reported Outcomes Measurement Information System
PI	Principal Investigator
PHI	Protected Health Information
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Clinical Trail
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event/Serious Adverse Experience
SDF	Silver Diammine Fluoride
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations For Interventional Trials
TSQM	Treatment Satisfaction Questionnaire For Medication
UP	Unanticipated Problem
US	United States
VAS	Visual Analogue Pain Scale
WHO	World Health Organization
WHO	World Health Organization
ZINB	Zero-Inflated Negative Binomial
ZIP	Zero-Inflated Poisson

PROTOCOL SUMMARY

Title:

Reducing Oral Health Disparities of Older Adults: Comparative Effectiveness of 2 Treatments

Précis:

The study is a cluster randomized clinical trial (RCT) to be conducted in 22 publicly subsidized housing facilities/sites (HUD Section 202) and other low-income housing voucher programs in NE Ohio. The facilities will be randomized to 2 arms: Arm 1 (11 sites) – Participants will receive biannual silver diamine fluoride (SDF) versus Arm 2 (11 sites): Participants will receive atraumatic restorative treatment (ART) with glass ionomer cement (GIC) + biannual fluoride varnish (FV) application. A total of 550 participants (Arm 1: 275, Arm 2: 275) will be followed for one year.

Objectives:

Primary: To compare the effectiveness of two evidence-based strategies, a "simple medical" strategy of topical application of SDF versus a "typical dental" strategy consisting of ART + FV given to older adults 62 and older to address (1) participant reported outcomes including tooth pain and hypersensitivity; and (2) clinical outcomes (caries arrest).

Secondary: To assess (1) participant reported outcomes (oral health quality of life, safety, and patient satisfaction); and (2) clinical outcomes (prevention of new decay).

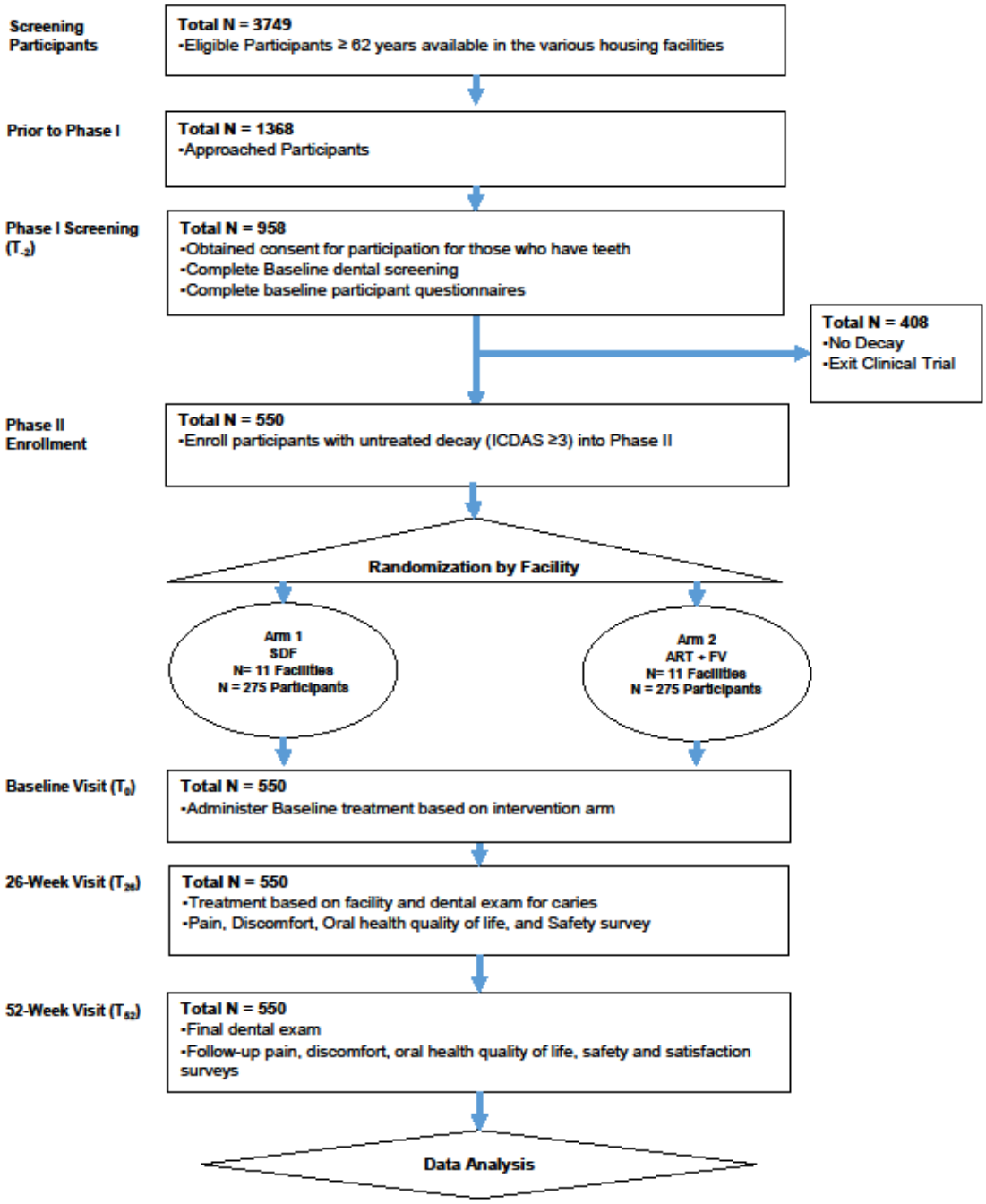
Population:

Population information: sample size = 550 older adults to be randomized; participants aged ≥ 62 years will be recruited from 22 subsidized housing facilities in NE Ohio, and will be randomized if they have at least one untreated active root or coronal carious lesion, and are willing to be in the study for 1 year. The socio-demographics of this population is expected to be a mean age of 74 years, 76% female, 51% Caucasian, 45% African-American, 2% Hispanic, and 2% other groups, 83% with two or more medical conditions.

Due to COVID-19 restrictions which prevented outside visitors/providers at the housing sites, approximately 40 enrolled individuals did not complete the 26 week visit/second dose of treatment. We will therefore increase the total number of enrolled participants by 40.

Phase:	III
Number of Sites:	22 independent living facilities for older adults, plus an additional *11* housing facilities to address some delays in recruitment due to the COVID-19 pandemic.
Description of Intervention:	The interventions for this study are in current clinical use. Two evidence-based strategies in older adults will be compared as follows: (Arm 1) a "simple medical strategy" consisting of SDF versus (Arm 2) a "typical dental strategy" consisting of ART + FV. We will attempt blinding of participants to the study group, but may not be possible due to SDF color change. The protocol for each arm will address both coronal and root surface tooth decay lesions: *Arm 1:* The treatment will be bi-annual topical 38% silver diamine fluoride (Advantage Arrest, Elevate Oral Care LLC., West Palm Beach, FL) following manufacturer's instructions and guidelines published by UCSF;[1] *Arm 2:* Atraumatic Restorative Treatment (ART) will be a modification of the approach used by Lo and colleagues (2006),[2] and the cavity restored with high viscosity glass-ionomer cement (GIC) (GC Fuji Automix LC Resin Reinforced Glass Ionomer Restorative, Japan)). Patients will also receive biannual topical fluoride varnish treatments (FluoriMax, Elevate) according to manufacturer's instructions.
Study Duration:	48 months
Subject Participation Duration:	12 months
Estimated Time to Complete Enrollment:	26 months

Schematic of Study Design:



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

The current U.S. health care system does not treat comprehensive dental care for adults as an essential health benefit under the ACA **(RQ-1)**.[3] Medicare excludes dental care and particularly for low-income individuals it leaves them with high out-of-pocket costs: 74% of the beneficiaries do not receive dental care annually.[4] The Institute of Medicine (IOM) recognizes that preventive oral care can reduce medical costs.[5]

Over 96% of all U.S. older adults aged ≥ 65 years have had caries experience in the permanent teeth. [6] Untreated tooth decay is disproportionately found in non-Hispanic Black (41%) and Hispanic (27%) compared to non-Hispanic white older adults (16%).[7] Consequently, tooth loss is also significantly higher in non-Hispanic blacks compared to other groups.[7] About 37% of adults ≥ 65 years have tooth decay in exposed root surfaces .[6] Caries is the primary cause of tooth loss in older adults, and tooth loss is inversely related to oral health related quality of life.[8] The progression of oral diseases adversely affects general health.[9] A recent 2018 oral health screening and survey of older adults highlights that many are living with significant untreated dental disease especially low-income seniors impacting their chewing, nutrition, and overall wellbeing that requires immediate attention and focus **(RQ-1)**. [10]

Our 2016-17 data on 202 older adults from 16 publicly subsidized housing units indicates untreated caries (58%) is two times higher than the national average (28%).[11] All had at least one medical condition, while 83% had two or more medical conditions **(RQ-4)**. Nationally, 92% of U.S. older adults have at least one medical condition, and 77% have ≥ 2 conditions.[12] Low-income U.S. older adults have disparately increased medical conditions compared to their more affluent counterparts[13] as shown by our NE Ohio data. Recent studies indicates that poor dental health (caries, periodontitis) was related to worsening glucose tolerance and an increased risk of diabetes,[14] and having fewer teeth/tooth loss and other patient reported oral health problems was associated with greater physical frailty in older adults.[15] Medical conditions lead to less frequent dental visits among older adults with cognitive impairment[16] and those with diabetes, with significant disparities among low-income groups. [17] Moreover, systemic conditions such as cardiovascular and respiratory disease, diabetes etc. have been associated with oral infections.[18] Untreated oral infection leads to pain, overuse of emergency visits, and even death **(RQ-1)**.[19]

Despite the profound impact of oral health status on quality of life,[9]many older adults accept their oral health problems as an inevitable process of aging and do not seek dental care.[20] In fact, ADA Health Policy Institute survey indicates that low perceived need (i.e. not needing dental care) was the top reason that older adults do not intend to visit a dentist.[21] This belief, further impacted by limited dental insurance options results in oral health becoming a low priority among older adults. The National Health Interview Survey 2014 data indicate that most older adults reported financial barriers to receiving dental care compared to any other type of health care.[22] A further challenge is that older adults have increased medical problems, physical frailty, and cognitive issues that challenge dental care access in this group.[23] Testing interventions provided outside of traditional dental offices will address barriers to seeking care among this population **(RQ-1, RQ-3)**.

Conventional restorative treatments do not work for older adults. The dental treatment needs of older adults differ from those of younger adults and thus makes diagnosis and treatment planning more complex due to age related changes to the enamel, dentine, and pulp chamber.[24]For this reason, results of work conducted in children cannot be extrapolated to older adults **(RQ-1)**. The majority of tooth decay in older adults is failure of restorations at the gum line and in exposed roots.[25] These lesions are difficult to diagnose or restore, even for experienced dentists.[23] A randomized trial in older adults with root caries treated the decayed tooth surfaces with either ART or conventional treatment (using a dental drill) and found that ART had a similar restoration survival rate (87% vs. 91%).[2] Fluoride varnish and SDF are also both effective in arresting and preventing new tooth lesions.[26]

Silver Diamine Fluoride (SDF) has been long used to arrest caries in other countries and is now widely available in the United States.[1] The liquid agent is painted on the decayed tooth or root and the treated lesion hardens, while the lesion depth decreases [27,28] and becomes resistant to caries bacteria.[29] SDF inhibits the decay process by restricting the bacterial metabolic and reproductive functions leading to bacterial killing. [30] Thus, silver is an antimicrobial that kills cariogenic bacteria far superior to other antimicrobial medicaments.[31] Annual 38% SDF has been effective in arresting and preventing root caries lesions among older adults in clinical trials.[32–34] Recently, the American Dental Association evidence-based clinical practice guidelines recommends bi-annual application of SDF on permanent teeth.[35]

Despite the greater dental caries burden, there are no community-based public health interventions that exist for low-income older adults like those for children, and the current clinic-based dental care delivery system is expensive and ill adapted **(RQ-1)**.[36] For any caries preventive/treatment intervention to be useful on a population level, 5 presumed attributes are necessary: pain and infection control, simplicity of use, cost affordability, minimal personnel time and training, and non-invasive.[37] Our proposed non-surgical interventions can meet this criteria and provide evidence **(RQ-5)**.

Therefore, we propose a cluster RCT to compare two non-surgical evidence-based strategies to address disparities in untreated tooth decay and dental care access **(RQ-2)**. The conventional surgical care using the “drill” and “fill” paradigm is not the best nor the most effective option for low-income older adults. Nationally, if only 26% of Medicare beneficiaries are seeking dental care annually in dental offices, our proposed interventions has the potential to reach a lot more older adults where they live in order to reduce oral health disparities.

2.2 Rationale

Comparative effectiveness studies of the proposed interventions are needed to inform the most effective community-based treatment strategy for older adults and to establish a standard of care **(RQ-1, SR-1)**. A systematic review and meta-analysis supports the use of SDF, [38,39] the use of ART with high viscosity glass ionomer cements (GIC),[40] and the use of fluoride varnish (FV)[41] for tooth decay management in older adults **(RQ-5)**. Thus, the proposed research compares commonly used evidence-based treatments.

Therefore, this study will determine the effectiveness of two relatively inexpensive, accepted non-surgical treatments that can be provided by dental hygienists (dental paraprofessionals) in

most states outside of traditional dental clinics to address the unique oral health needs of low-income older adults **(RQ-1)** i.e. a "simple medical" strategy using bi-annual application of SDF and a "typical dental" more complex strategy consisting of ART and biannual application of FV. The rationale is that providing conventional (surgical with a drill) treatment actually exacerbates disparities because such treatment is resource intensive and is relatively ineffective. Our hypothesis tests that the "medical" strategy is not less effective as the "dental" strategy in caries arrest and prevention.

Further, our focus is on low-income older adults residing independently in Housing and Urban Development (HUD) and other publicly subsidized housing facilities with limited access to dental care. In particular, we will focus on subgroups of older adults with co-existing medical conditions as these individuals are most likely to experience disparities **(RQ-4)**. The non-surgical treatment strategies were selected based on scientific evidence and the feasibility of application by licensed paraprofessionals in community-based settings as this can address multiple barriers to dental care and subsequently increase access for low-income older adults **(RQ-5)**. Both approaches are now used in traditional dental clinics along with conventional intensive dental care. Our outcomes address the concerns of older adults (based on surveys, interviews, and prior studies of this population) that include: tooth decay, and participant reported tooth pain, hypersensitivity, and decreased quality of life **(RQ-3, RQ-6, PC-1)**.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Study Interventions: SDF was introduced in the US in 2015 and approved by the FDA as a medical device; the high viscosity glass ionomer cements (GIC) used in ART were introduced in the 1970s. All of the interventions are in current clinical use for package inserts for SDF, ART with GIC, FV). The study interventions are non-invasive and does not require the use of conventional drilling procedures. There is risk of hypersensitivity to silver or fluoride from the 38% SDF. SDF can stain the gums or oral mucosa or tooth colored fillings. There is minimal risk with the ART and FV applications **(RQ-5)**.

Dental exams: The project will involve clinical dental exams for the participants. The dental exams do not pose any additional risks to participants beyond those encountered in daily living. Dental examinations will be visual/tactile using a probe and non-invasive. No x-rays will be taken.

Interviews: Some people are uncomfortable answering questions about themselves for research. We will try to make participants feel as comfortable as possible. There is also a chance that confidential information can be lost but we will use every precaution to protect the information. To protect the privacy of participants, a unique ID number will be used. The connection between this code number and participant's identity will be confidential and will be required to link the contact form, questionnaires and dental data. Only project staff members will have access to these codes and identifying information. Once the study data collection is completed, the link between the individual and their data will be destroyed.

Focus groups: There is little risk to participants during the focus group discussions. While it is unlikely, some participants may feel shy or embarrassed by some of the questions asked during the meetings or interviews. The facilitator and moderator will make every effort to put participants at ease and to communicate to them that any information shared during the discussions and interviews would not be relayed to others. Further, any names or other identifying information will be removed during the transcription process and will not appear in the final transcripts of the discussion groups. All audio files will be deleted after they are transcribed.

2.3.2 Potential Benefits

Participants may benefit from the SDF and ART + FV treatment applications in the arrest of caries and in patient-reported pain and oral health quality of life symptoms Society may benefit from the knowledge gained about the comparative effectiveness of a simple topical medical treatment (SDF) versus a typical dental treatment. The findings from the proposed study will be useful for patients and providers. Patients can make informed decisions regarding the evidence-based non-surgical options that are available for treating decay, reducing tooth pain, and improving quality of life.

Providers will use the findings to establish standard of care for older adults with unique dental issues, co-morbid conditions, frailty, and dementia. Long-term having an effective standard of care will reduce oral health disparities for older adults with limited resources. Further, delivering dental care in community-based settings will be instrumental in treating far more older adults than the current dental office-based care. This will address the national disparity gap and the limited dental insurance options for older adults.

There will be no direct benefit to the participants in the focus groups, but taking part in group discussions could have indirect or incidental benefits for respondents. These might include the social stimulation of the discussion process, or the knowledge that their participation could help in disseminating the findings to other populations.

Older adult respondents will receive a tooth care kit (free toothbrushes, toothpaste, floss) to facilitate good oral hygiene. On balance, we believe any potential risks are reasonable in relation to the anticipated benefits to research participants and others.

3 OBJECTIVES

3.1 Study Objectives

Primary objective:

1) To investigate the comparative effectiveness of two evidence-based strategies in low-income older adults ≥62 years old followed for one year: (Arm 1) a “simple medical” strategy of bi-annual topical application of silver diamine fluoride (SDF) versus (Arm 2) a “typical dental” strategy consisting of atraumatic restorative treatment (ART) + bi-annual application of fluoride varnish (FV).

2) To examine the narratives of subgroups of publicly subsidized housing participants to understand their experiences with non-surgical regimens and identify ways to improve and disseminate in other community-based settings nationally.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

Primary outcomes are: (1) participant reported outcomes including tooth pain and hypersensitivity, and (2) clinical outcomes (caries arrest). Clinical outcomes will be assessed through dental exams conducted by calibrated examiners. Participant questionnaire will assess patient-reported outcomes using validated instruments. All primary outcomes will be measured at baseline, 26 & 52 weeks.

3.2.2 Secondary Outcome Measures

Secondary outcomes are: participant reported outcomes (oral health quality of life); and clinical (prevention of new decay). All secondary outcomes will be measured at baseline, 26 & 52 weeks.

3.2.3 Mediators, Process Outcomes

Moderator variables are: socio-demographics, medical/physical conditions, oral health behavior that will be collected at baseline (prior to treatment).

Process outcomes are: Safety measure that will be collected at 2, 26 & 54 weeks, and satisfaction survey with the treatment will be assessed at 54 weeks.

4 STUDY DESIGN

This study is a cluster randomized clinical trial to assess the comparative effectiveness of two caries treatment interventions for individuals residing in 22 publicly subsidized housing facilities/sites (HUD Section 202) and other low-income housing voucher programs in NE Ohio **(RQ-2)**. Each facility will be randomized to 2 arms:

Arm 1 (11 facilities) – A total of 275 participants from these facilities will receive biannual SDF.

Primary Hypothesis: Simple medical treatment (Arm 1) is non-inferior to typical dental treatment (Arm 2) for clinical (caries arrest) and patient-reported (tooth pain/hypersensitivity) at 12-months post treatment.

Arm 2 (11 facilities): A total of 275 participants from these facilities will receive ART + biannual FV application.

Secondary Hypothesis: Simple medical treatment (Arm 1) is non-inferior to typical dental treatment (Arm 2) for clinical (new decay) and patient-reported (oral health quality of life) outcomes at 12-months post treatment.

The participants will be recruited over a *three*-year period, and each participant will be followed for one year (total of 3 visits -baseline, 26 weeks, 52 weeks). All participants will receive a dental screening and prophylactic cleaning at all visits. The proposed interventions will address the high burden of untreated tooth decay in community dwelling low-income older adults and thus reduce disparities **(RQ-5)**. The non-surgical interventions can be provided by paraprofessionals. We have previously worked in these housing facilities and understand the logistics of recruiting and conducting clinical dental exams on-site **(PC-1)**.

The randomization is at the level of the cluster (housing facility) for logistical efficiency. This will greatly reduce the potential for error that could otherwise occur with people at the same site assigned to different treatments. Furthermore, keeping the same treatment at each site reduces chances of 'contamination' (i.e. participant discussing their treatment with others). Additionally, stratified cluster randomization will be used, i.e. a block (constrained) randomization approach in which balance over treatments is assured for 2 key cluster-level (stratification) variables, namely facility size (>100 versus ≤100 residents), and geographic location (Cuyahoga County vs other **(RQ-5, RC-2, RC-5)**.

4.1 Study Participants (RQ-3, RQ-4, PC-2)

Subjects will be low socioeconomic status (SES) adults ≥ 62 years of age in NE Ohio counties (Cuyahoga, Lorain, Summit, Ashtabula, Geauga, and Lake) residing in 22 participating HUD Section 202 and other publicly subsidized housing facilities (see table 1). The population is diverse: African American/Black, Caucasian/White including Hispanic/Latino, and Asian. Medicaid participation among the tenants is 76% among facilities. From our prior study in these facilities, mean age is 74 years, 76% female, 51% Caucasian, 45% African-American, 2% Hispanic, and 2% other racial/ethnic groups; 60% of HUD older adults had none/rare dental visits in over 3 years. The study will be offered to all older adults if they are aged ≥ 62 years, reside in the 22 housing facilities, have at least one natural tooth and be willing to stay in the

study for 1 year. Only those with severe medical, cognitive or motor impairments will be excluded. To be eligible for enrollment in the clinical trial phase of the study, at the baseline dental exam, subject must have at least one untreated active root or coronal carious lesion with ICDAS-II lesion severity code of 3 or greater.

Table 1. Facilities Enrolled in the Clinical Trial

Facility Name*	**# of tenants**	**Name of Individual Providing Letter of Support (Agency)**	**Type of Community**	**County**
Westerly Apartments	455	Linda Sack (Westerly Apartments)	suburban	Cuyahoga
St. Timothy Manor	40	Susan Fine (Humility of Mary Housing)	suburban	Cuyahoga
St. Timothy Park	40	Susan Fine (Humility of Mary Housing)	suburban	Cuyahoga
Villa at Marion Park	40	Sr. Mary Slattery (Humility of Mary Housing)	urban	Summit
St. Patrick Manor	50	Juanita Arnett (Humility of Mary Housing)	suburban	Lorain
Jennings Manor, Library Court, St. Rita, St. Agnes	220	Jim Patena (Jennings)	suburban	Cuyahoga
Margaret Wagner	60	Rosalind Mitchell (Benjamin Rose Institute)	urban	Cuyahoga
Willowood Manor	74	Sandra Milos (Willowood Manor)	suburban	Cuyahoga
Knickerbocker	168	Carryeanne Smitley (Knickerbocker)	suburban	Cuyahoga
Abington Arms	157	Susan Persing (Abington Arms)	urban	Cuyahoga
Fedor Manor	145	Sandra Rodriguez (Fedor Manor)	suburban	Cuyahoga
Ambleside Tower	201	Kristie Groves (CMHA)	urban	Cuyahoga
Severance Tower	188	Kristie Groves (CMHA)	urban	Cuyahoga
Cedar Highrise	155	Kristie Groves (CMHA)	urban	Cuyahoga
Addison Square	225	Kristie Groves (CMHA)	urban	Cuyahoga

Apthorp Tower	166	Kristie Groves (CMHA)	urban	Cuyahoga
Euclid Beach Gardens	149	Kristie Groves (CMHA)	urban	Cuyahoga
Bohn Tower	267	Kristie Groves (CMHA)	urban	Cuyahoga
Riverview Tower	498	Kristie Groves (CMHA)	urban	Cuyahoga
King Kennedy	91	Kristie Groves (CMHA)	suburban	Cuyahoga
Quarrytown	180	Kristie Groves (CMHA)	suburban	Cuyahoga
Franciscan Village	180	Catherine Sabolik (Franciscan Village)	urban	Cuyahoga
Total # of Tenants	**3749**			
*Average Medicaid: 76%				
Additional 11 sites added with modification				
Carnegie Tower at Fairfax	171	Tara Wenger	Urban	Cuyahoga
Mother Teresa Manor/Commons	99	Tara Wenger	Suburban	Cuyahoga
Educator Senior Housing	112	Linda Sack	Urban	Cuyahoga
Lorain Square	110	Kristie Groves (CMHA)	Urban	Cuyahoga
Beachcrest	235	Kristie Groves (CMHA)	Urban	Cuyahoga
Villa Serena	*242*	*Vesta Corp MOU*	*Suburban*	*Cuyahoga*
Helen S. Brown	*64*	*Chase Pesina*	*Urban*	*Cuyahoga*
Greater Abyssinia Tower	*69*	*Angela Jackson*	*Urban*	*Cuyahoga*
Mt. Auburn Manor	*107*	*Kristie Groves (CMHA)*	*Urban*	*Cuyahoga*

Mildred Brewer	*39*	*Kristie Groves (CMHA)*	*Urban*	*Cuyahoga*
La Ronde	*57*	*Kristie Groves (CMHA)*	*Urban*	*Cuyahoga*

The 22 housing facilities for this study are located in Northeast Ohio counties. We have formed relationships with administration of HUD and Regional Housing Authorities to ensure these sites are available. All 22 facilities were carefully chosen to ensure accurate representation of the northeast Ohio region. Twelve facilities are located in large metropolitan areas, while 6 are in inner ring and 4 are in outer ring suburbs or rural areas.[42] All facilities are publicly subsidized through United States Department of Housing and Urban Development (HUD) programs geared toward seniors with limited financial resources. Several public and private housing authorities and management agencies oversee the facilities in our sample, each with multiple housing units located throughout the northeast Ohio region. This network of agencies will be of value when communicating results and for possible further implementation.

4.2 Model and Design

Figure 4.2.1 shows the study model for the intervention. The comparative effectiveness of "simple medical", i.e. SDF versus "typical dental", i.e. atraumatic restorative treatment (ART) + fluoride varnish (FV) intervention in this study is focused on the person level to address the unique oral health needs of low-income older adults. Figure 1 indicates that the proposed intervention is hypothesized to arrest caries in older adults with untreated caries and prevent tooth pain/hypersensitivity (primary outcomes); prevent new decay and improve oral health-related quality of life (secondary outcomes) over a 12-month follow-up period. Safety and satisfaction measures are process outcomes that are critical to assess for sustainability and dissemination of the interventions. Factors likely to moderate the effectiveness of interventions are socio-demographics, chronic medical conditions, and oral health behavior. These baseline (pre-treatment) variables are also considered as prognostic variables (related to outcomes). Additionally, 3 focus groups (≈ 8 to 10/group) of study participants in years 2, 3, and 4 will be conducted to understand experience with treatment and find ways of improvement.

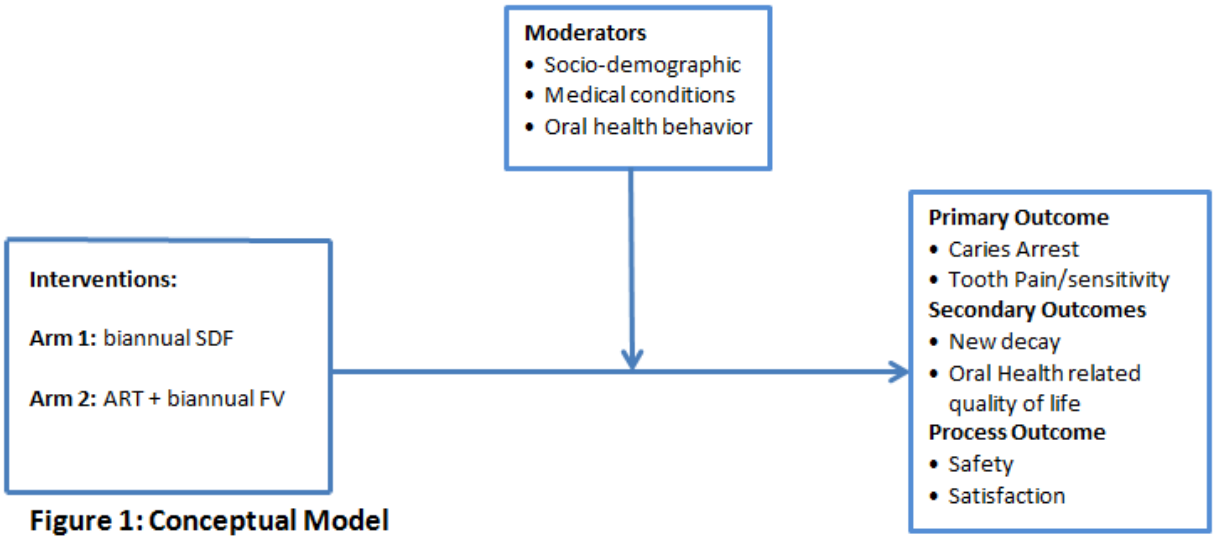

Figure 1: Conceptual Model

Interventions to be tested:

The interventions proposed for this study are in current clinical use. Both coronal and root surface tooth decay lesions will be treated. The two evidence-based strategies in older adults will be compared as follows:

Arm 1 (N=275 participants): A "simple medical strategy" consisting of SDF

The treatment will be bi-annual application (at baseline and 26 weeks) of topical 38% silver diamine fluoride (Advantage Arrest, Elevate Oral Care LLC., West Palm Beach, FL) following manufacturer's instructions and guidelines published by UCSF.[43]

Arm 2 (N=275 participants): A "typical dental strategy" consisting of ART + FV

Atraumatic Restorative Treatment (ART) will be a modification of the approach used by Lo and colleagues (2006),[2] and the cavity restored at baseline with resin reinforced glass-ionomer cement (GIC) (GC Corporation, Japan).

Participants in this arm will also receive biannual topical fluoride varnish application (FluoriMax, Elevate) according to manufacturer's instructions.

Modifications Made Due to COVID-19

Due to COVID-19 restrictions which prevented outside visitors/providers at the housing sites, recruitment will take longer than the anticipated 24 months. Additionally, approximately 40 enrolled individuals did not complete the 26 week visit/second dose of treatment. We will therefore increase the total number of enrolled participants by 40. We are also adding four additional housing facilities to the study to address some delays in recruitment due to the COVID-19 pandemic. These four sites are managed by National Church Residences.

The additional 4 sites will also be randomized to Arm 1 and Arm 2 for a total of 13 sites in each arm.

5 STUDY ENROLLMENT AND WITHDRAWAL

The *original* 22 housing facilities have a total of 3749 tenants 62 years and older, therefore, we will approach 1368 participants, out of whom 958 will be screened for cavities to obtain the target sample of 550 older adults (approx. 25/housing facility) who have at least one natural tooth. Only individuals with severe medical, cognitive or motor impairments will be excluded. Individuals living independently (our study population) will likely not have severe impairments. Severe medical and motor impairments preventing enrollment will be those which would prevent the individual from completing the dental screening. Severe cognitive impairment will be determined through the consent process. If an individual is unable to explain back to the person obtaining consent what the study involves and what they will do, they will not be consented. Recruitment efforts for the main trial will take place over a two-year period. The study staff will approach tenants at various venues and inquire if they are completely edentulous to check study inclusion/exclusion criteria. Following are the estimates based on our prior study: 73% had at least one tooth; 70% providing consent; 58% with untreated caries. We expect a target of 550 participants to be randomized to the two arms.

The recruitment for all housing sites will follow a 2-stage process: (1) all participants consented will participate in the dental screening; (2) participants found to have non-urgent cavities at the screening and who fulfill the inclusion criteria will be enrolled into the clinical trial.

5.1 Subject *Initial* Inclusion Criteria

In the first stage of the enrollment process, an individual must meet all of the following criteria:

- Provide signed and dated informed consent form
- Willing to comply with all study procedures and be available for the duration of the study (1 year)
- Male or female, aged 62 years or older
- Live in a participating older adult housing facility

In the second stage of enrollment process, additional inclusion criteria for continuation and participation in the RCT is based on the dental screening:

- Have at least one untreated root or coronal caries lesion on any permanent tooth with an International Caries Detection and Assessment System (ICDAS) II[44] active lesion score of 3 or greater (localized enamel cavity to extensive cavity).

5.2 Subject Exclusion Criteria

Following the dental screening, further exclusion criteria for non-eligibility to participate in the RCT include:

- Sensitivity to silver or other heavy-metal ions
- Those with ulcerative gingivitis or stomatitis which prevents them from receiving study treatment
- Serious life-threatening medical disease

5.3 Strategies for Recruitment and Retention

We will use prior successful strategies in recruiting and also solicit input from our stakeholders. Strategies that will be used are as follows: Service coordinators at all 22 facilities will serve as site liaisons. The study PI/project manager will provide the service coordinators with an introductory letter/flyer containing study information to be given to tenants and to be posted in public areas of the facility. Service coordinators will first arrange an informational meeting (study dentist will give a talk on the interventions as suggested by our stakeholders), and will arrange a second recruitment meeting for study staff to present information regarding the study at scheduled group events (e.g. tenant meetings, health fairs). For planning purposes, service coordinators will have a sign-up sheet for those interested in the sessions. Study staff will schedule those who are interested and meet the inclusion criteria for one-on-one sessions at the housing facility to obtain informed consent and collect baseline survey data. Baseline dental exam and treatment appointments will then be scheduled at each facility according to a designated exam day(s) for each facility, which will occur approximately 1-2 weeks following consent and baseline data collection. Six and twelve month dental exams/treatment and one-on-one interviews for follow-up survey completion for each time point will also occur at the housing facility where participants reside

Retention strategies for participants will include:

- Participants will be given promotional items (i.e. pens, magnets) with the study logo and contact phone number at recruitment.
- Alternate contact information for family/friends that may be able to reach the participant if primary contact information becomes invalid will be obtained at recruitment.
- Annual birthday/holiday cards will be sent to participants to maintain contact.
- Newsletters will be sent twice a year with updates on the study's progress (i.e. recruitment), and a reminder to update their contact information (by phone or mail).
- Assistance from service coordinators or other facility staff will also be solicited for hard to reach/contact participants.
- *Due to COVID-19 delays, an additional 4 housing sites are being added to the study to accelerate recruitment.*

5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures (RQ-2)

Randomization is at the level of the cluster (housing facility) for logistical efficiency. This will greatly reduce the potential for error that could otherwise occur with people at the same site assigned to different treatments. Furthermore, keeping the same treatment at each site reduces chances of 'contamination' (i.e. participant discussing their treatment with others). Additionally, stratified cluster randomization will be used, i.e. a block (constrained) randomization approach in which balance over treatments is assured for 2 key cluster-level (stratification) variables, namely facility size (>100 versus ≤100 residents), and geographic location (Cuyahoga County vs other). The project statistician, Dr. Albert will generate the randomization scheme for the 22 + *4 additional* housing facilities. While the randomization is at the housing level, the study objectives, interventions and primary outcomes all pertain to the individual level **(RC-1).**

5.4.2 Masking Procedures (IR-6)

We will attempt blinding of participants to the study group, but this may not be possible due to SDF color change.

The hygienists will be unaware of the treatment assignment when they go to their respective housing facilities. For all treatment visits, assessments will be conducted prior to the intervention delivery.

Two hygienists will go to the housing facility randomized to the SDF arm and the other two will go to the ART + FV arm. The baseline treatment to be applied will be revealed only after the baseline caries exam has been completed. At the 6 month follow-up visit, the two hygienists that applied SDF will now go to the facilities randomized to the ART + FV facilities and vice-versa to conduct the 6-month follow up caries assessment exam and treatment. We will follow similarly for the 12-moth follow-up visit. By this strategy, we will make sure that potential bias of the hygienist evaluating their own work is minimized. Additionally, periodically we will check for the quality of the assessment data by Dr. Pinto randomly examining 20% of the participants.

5.5 Subject Withdrawal

5.5.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request, as outlined in the consent form documents.

Participants who drop out (or withdraw) from the study by their own choice will be considered dropouts/withdrawals. Participants who are discontinued from the study by one of the study personnel will be also be considered a dropout/withdrawal.

An investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.

- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

All reasons for dropout/withdrawal or discontinuation of the study intervention will be documented in the tracking database and reviewed by the study team and reported to the DSMB. For gathering information on discontinuation, study staff will be contacting participants at several time points. Study staff will contact participants by phone 2-3 days before all exam and treatment visits to remind participants of the appointment, 2-3 days before all one-on-one interview appointments for survey completion, and 24 hours after all dental exam and treatment visits to complete the safety questionnaire. Participants will also be seen in person for all exam and treatment appointments and one-on-one interview appointments for survey completion.

In the event of a subject telling study staff that he/she is dropping out of the study, the study staff should gather the following information as much as the participant allows.

- Record the reason for dropping out of the study.

- Record any adverse event reported by the subject.

- Complete the appropriate questionnaire nearest the drop out time point.

If it is determined by study staff that a participant should be discontinued from the study, the decision to withdraw a participant must be discussed and confirmed by the PI.

Participants that withdraw during the baseline data collection window will be replaced by recruitment of additional participant to reach enrollment goals. Participants that withdraw or that are lost to follow-up any time after the baseline data collection window will not be replaced, but data collected up to the point of withdrawal will be used for analysis.

5.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the Investigational New Drug (IND) /Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.

- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

6 STUDY INTERVENTION

6.1 Study Product Description

None of the materials used in this study are experimental. All materials are cleared by the FDA as Class II medical devices. All of the study materials will be donated by the manufacturers.
Study Arm 1:

- Advantage Arrest. This is an aqueous solution of 38% silver diamine fluoride, tinted blue.

Study Arm 2:

- GC Fuji Automix LC. This is a radiopaque light cured resin reinforced glass ionomer restorative.
- Cavity Conditioner. Mild aqueous polyacrylic acid solution
- GC Fuji COAT LC. This is a light cured protective coating.
- FluoriMax Varnish. This is sodium fluoride in an alcohol solution of natural resins.

6.1.1 Formulation, Packaging, and Labeling

Study Arm 1:

- Advantage Arrest. This is an aqueous solution of 38% silver diamine fluoride, tinted blue. Packaging and labeling are not modified from the commercial product. This product is packaged in individual dosettes, with one dosette used per patient.

Study Arm 2:

- GC Fuji Automix LC. This is a paste/paste formulation that is packaged in the original automix syringe. Packaging and labeling are not modified from the commercial product. Each syringe is expected to provide about 10 restorations.
- Cavity Conditioner. Dispensed in a 5.7 ml multi-use vial. Packaging and labeling are not modified from the commercial product.
- GC Fuji COAT LC. This is a light cured protective coating. Packaging and labeling are not modified from the commercial product. Each bottle holds 5.2 ml of product.
- FluoriMax Varnish. This is sodium fluoride in an alcohol solution of natural resins. Packaging and labeling are not modified from the commercial product. This varnish is packaged in individual dosettes, with one dosette used per patient.

6.1.2 Product Storage and Stability

Study Arm 1:

- Advantage Arrest. Product is to be stored in a cool, dark place (4-25 C). It has a shelf life of 3 years from the date of manufacture. Individual dosettes should be discarded after use.

Study Arm 2:

- GC Fuji Automix LC. Product is to be stored in a cool, dark place (4-25 C). It has a shelf life of 2 years from the date of manufacture.
- GC Fuji COAT LC. Product is to be stored in a cool, dark place (4-25 C). It has a shelf life of 2 years from the date of manufacture.
- Cavity Conditioner (GC). Product is to be stored in a cool, dark place (4-25 C). It has a shelf life of 3 years from the date of manufacture.
- FluoriMax Varnish. Product is to be stored in a cool, dark place (4-25 C). It has a shelf life of 3 years from the date of manufacture. Individual dosettes should be discarded after use.

6.2 Dosage, Preparation and Administration of Study Product

Study Arm 1:
Advantage Arrest. The application procedure is below:

1. The cavity will be cleaned with a dry manual tooth brush to remove debris.
2. The area will be isolated with cotton rolls. If the lesion is at the gumline, the gingiva will be coated with a thin layer of petroleum jelly per manufacturer's instructions.
3. The single use SDF vial (Advantage Arrest, Elevate Oral Care) will be opened and the manufacturer's supplied brush will be dipped into the reservoir. The SDF will be applied with the brush until the lesion is coated fully.
4. Allow to air dry. The patient can resume normal activity with no restriction.

Study Arm 2:
GC Fuji and Advantage Arrest. The application procedure is below:

1. The cavity will be isolated and dried
2. Any debris and soft, demineralized tooth structure from cavitated lesions will be removed with spoon excavators as necessary and protecting the pulp. No local anesthesia will be used.
3. The cavity will be cleaned next with a *manual* brush and pumice or a toothbrush or cotton roll.

4. Application of polyacrylic acid conditioner to the cavity and rinsing (Cavity Conditioner (GC)).
5. The area will be moisture controlled before placement of resin reinforced glass ionomer restoration (GC Fuji Automix LC) with an applicator gun. Next the finger will be used to compress the material into the cavity.
6. After the GIC material is placed, GC Fuji COAT LC will be used.

7. The occlusion will be checked and cleared using articulating paper.
8. The GIC application will be light cured.

More details about the step by step procedure is given in Section 6.10.

6.3 Modification of Study Product Administration for a Subject

The study products' administration are not being modified.

6.4 Accountability Procedures for the Study Product

The study products will be stored in a locked storage area. The principal investigator (or her delegate) will maintain an inventory system to account for study products. The products will be distributed before each clinic session and unused product will be maintained in the field units. The materials will only be used by licensed personnel.

6.5 Assessment of Subject Compliance with Study Product Administration

The principal investigator (or her delegate) will check the inventory against the inventory records once per month. Any deviation will be documented.

6.6 Concomitant Medications/Treatments

The study will collect information on concomitant medications by patient self-report at exam and again at the final clinical examination. Of particular concern to the validity of study results will be use of fluoridated toothpaste, over the counter fluoride rinses or gels, professionally administered fluorides, antibiotics, and medications used to counter dry mouth conditions. There are no medication exclusion criteria.

6.7 Administration of Intervention

Arm 1: Topical application of 38% silver diamine solution to ICDAS lesions code 3-6.
Arm 2: Atraumatic Restoration Treatment (ART) to ICDAS lesions code 3-6, followed by topical fluoride varnish (FV) to all teeth.

6.8 Procedures for Training Interventionists and Monitoring Intervention Fidelity

The study interventionists (dental hygienists) will receive didactic and clinical instruction on administration of the clinical interventions. The hygienists will undergo a two-day training and calibration exercise with extracted teeth and applying the intervention on patients. The didactic instruction will include required reading, viewing of technique videos, and laboratory and clinical practice. The supervised laboratory practice will use extracted teeth in which there are natural or instructor created cavities. The clinical application will be practiced on at least one patient.

To be certified, the study interventionist must demonstrate mastery. For ART and FV application the trainee will complete a written or oral exam on procedures (from set up to cleanup); Complete no less than 8 ART on the lab bench on extracted teeth; Complete no less than 3 ART on an older adult patient with cavities; Complete at least one FV treatment on the same patient. For SDF the trainee will complete a written or oral exam on procedures; complete at least 1 treatment on an extracted tooth; complete at least 1 treatment on an older adult patient. During the actual intervention visits to the housing facility, the study dentist will be present to supervise the hygienists to make sure that the study treatment were delivered per protocol. If there is a problem with the delivery of the treatment or adherence to protocol then the

interventionists will be given corrective training. *For 52 week follow-up visits, where treatment will not be delivered, the study dentist may not be present.*

6.9 Assessment of Subject Compliance with Study Intervention

In addition to direct supervision, the interventionist will use clinical photographs to capture random images of ART restorations. These will be reviewed on a quarterly basis by the clinical dentist supervisor/gold standard trainer and corrective training will be provided if there is a problem with clinician compliance. All deviations of protocol will be documented.
The clinical dentist supervisor will observe the application of the various study materials for each of the interventionists. Corrective training will be provided if there is a problem with clinician compliance. All deviations of protocol will be documented.

6.10 Study Procedural Intervention(s) Description

There is no product masking in this study.

Study Arm 1:

Advantage Arrest. The application procedure is below:

1. The cavity will be cleaned with a dry manual tooth brush to remove debris.
2. The area will be isolated with cotton rolls. If the lesion is at the gumline, the gingiva will be coated with a thin layer of petroleum jelly per manufacturer's instructions.
3. The single use SDF vial (Advantage Arrest, Elevate Oral Care) will be opened and the manufacturer's supplied brush will be dipped into the reservoir. The SDF will be applied with the brush until the lesion is coated fully.

4. Allow to air dry. The patient can resume normal activity with no restriction.

Study Arm 2:

Application procedure for the atraumatic restorative treatment is as follows::

1. When the lesion is on the occlusal surface, the occlusion will be checked with blue articulating paper prior to other clinical procedures.

2. The field will be isolated with cotton rolls. Soft debris will be removed with moistened cotton pellets. Then soft demineralized tooth structure will be removed with a spoon excavator at the periphery of the lesion, where there is access. A *manual* brush and pumice will be used to remove any further loose material. The cavity will be washed well with water.

3. The cavity will be conditioned with the liquid of the glass ionomer (polyacrylic acid) for 10-15 seconds and then rinsed, maintaining moisture control throughout.

4. The resin reinforced glass ionomer restorative (Fuji II LC Automix, GC America) will be inserted into the cavity using the manufacturer's delivery device and then coated with Fuji Coat (GC America). The restoration will then be light cured for 20 seconds.

Following the restorative treatment, the patient will be treated with fluoride varnish, as below.

FluoriMax Varnish. By quadrant or arch, all of the teeth will be coated with fluoride varnish (FluoriMax, Elevate Oral Care) using the manufacturer's brush system. The varnish container will be shaken for a few seconds before application. A single application from posterior to anterior will be used and then the occlusal surfaces will be coated, with no reapplication. The material will be allowed to dry 3-5 seconds and the patient instructed to avoid eating or dental hygiene for 4 hours.

If a participant reports any issue with the applied treatment within one week of the treatment date, the study team will return to the housing facility to examine and correct the treated tooth as needed. Within 48 hours, the study team will call the participant to ask the participant if the issue has been resolved and will administer a paper safety questionnaire. The completed paper safety questionnaire will be stored in the CRF folder and documentation of the return visit/treatment will be added to the participant's electronic record.

6.11 Administration of Procedural Intervention

Arm 1(SDF): SDF will be administered by a licensed dental hygienist at the baseline visit, and the 26-week visit.

Arm 2(ART +FV): ART will be administered by a licensed dental hygienist at the baseline visit + Fluoride Varnish application at baseline and the 26-week visit. If ART requires scooping out the decay then a licensed dentist will scoop the decay and then have the hygienist complete the ART intervention*. For 52 week follow-up visits, where treatment will not be delivered, the study dentist may not be present.*

7 STUDY SCHEDULE

Prior to any of the following actions, facilities will be randomized into one of two treatment intervention arms.

Refer to Appendix A for the Schedule of Events.

Temporary COVID-19 pandemic procedures:

Recruitment/Enrollment

- Study staff will receive contact information from Service Coordinators/Housing Managers for those who are interested in the study.

- Study staff will contact interested individuals by phone or video-conference and send them paper consent forms. They will review the consent form with the individual by phone or video-conference and answer any questions they may have and ensure the individual understands the study and all study procedures.

- Individuals will then be asked to sign the consent form and mail it back to the study staff in a stamped, self-addressed envelope provided to them. Study staff will sign the form and send a copy of the signed form back to the individual, along with a paper copy of the surveys.

- Study staff will then contact the individual by phone or video-conference to complete the surveys. Individuals will be asked to follow along on the paper survey while study staff reads the questions to them over the phone or video conference. Participant responses will be entered into REDCap by study staff during the phone call or video-conference.

- Exam/treatment appointments will be scheduled once the housing sites, funding agencies, IRB and CWRU have approved study personnel returning to being on-site at the housing sites.

26 and 52-week Follow-Up Data Collection

- Study staff will contact individuals due for the 26 *and 52*-week follow-up survey, to arrange a time to complete the survey by phone. Study staff will mail the survey to the individual prior to the survey completion phone call.

- Study staff will then contact the individual by phone at the scheduled time to complete the surveys. Individuals will be asked to follow along on the paper survey while study staff reads the questions to them over the phone. Participant responses will be entered into REDCap by study staff during the phone call.

- 26-week and 52-week exam/treatment appointments will be scheduled once the housing sites, IRB and CWRU have approved study personnel returning to being on-site at the housing sites

Once the COVID-19 pandemic ends, we will follow the original proposed plan.

Temporary COVID-19 pandemic procedures <u>for returning to in-person visits</u>:

During this time, housing sites will determine the best location for study activities, including exams/treatment, for their facility. This location may be located in areas indoors and/or outdoors at the facility.

The number of research staff attending on-site recruitment/data collection and dental screening/treatment appointments will be kept to a minimum. Only personnel essential for completion of the appointments will attend.

Research staff will complete a screening questionnaire on a daily basis using the CWRU Daily Health Assessment (if they are reporting to campus at any time during the day) or the ADA COVID-19 Employee Screening Log (if they are reporting only to a study site) to determine work readiness. Research staff will wear appropriate PPE as determined by their work function (mask, gloves, face shields, gowns, and head covering). All research staff will wear masks at all times and will perform proper hand hygiene while on-site at the housing facilities.

<u>Scheduling Procedures for Recruitment, Data Collection and/or Dental Exam/Treatment appointments at the housing sites</u>:

- For recruitment of new participants, research staff will obtain interested individual's contact information so they may contact them by phone to explain the study and administer the COVID-19 Screening Questionnaire prior to setting up a one-on-one meeting.
- All participants will be called by a research staff member and interviewed using the COVID-19 Screening Questionnaire.
- If the COVID-19 Screening Questionnaire is NOT passed (temperature >*100.0*, participant experienced any of the symptoms assessed, an/or participant has tested positive for COVID-19 or been in contact with someone who has tested positive for COVID-19), the participant will NOT be scheduled at this time.
- If the COVID-19 Screening Questionnaire is passed (no temperature >*100.0*, no reported symptoms, and no positive COVID-19 test or contact with a positive COVID-19 patient), participants will be scheduled for an individual appointment and will be instructed to stay in their apartments on the day of the appointment until called by project staff.
- Participants will also be instructed during this call of all procedural changes which will take place on the day of their scheduled appointment.

<u>Appointment Day Procedures for Recruitment, Data Collection and/or Dental Exam/Treatment</u>:

<u>Prior to the appointment</u>:

- Research staff will call participants to be reassessed using the COVID-19 Screening Questionnaire.
- If the COVID-19 Screening Questionnaire is NOT passed (temperature >*100.0*, participant experienced any of the symptoms assessed, an/or participant has tested positive for COVID-19 or been in contact with someone who has tested positive for

COVID-19), the participant will NOT be seen for their appointment at this time. They may be reassessed after 14 days.

- If the COVID-19 Screening Questionnaire is passed (no temperature >*100.0*, no reported symptoms assessed, and no positive COVID-19 test or contact with a positive COVID-19 patient), participants will be asked to come to the facility designated area for their individual appointment.
- If scheduled for a dental exam, participants will be asked to brush their teeth thoroughly and to use a mouth rinse if possible.
- All participants will be asked to wear a mask of their own into the facility designated meeting/exam area. If a participant does not have a mask, one will be provided to them.

At the appointment:

- Research staff will take and record participant's temperatures when they arrive for their appointment to determine if he/she may participate. If the recorded temperature is > *100.0*, the participant will NOT be examined/interviewed. They may be reassessed in 14 days.
- If the participant's temperature is < *100.0*, he or she may be interviewed/examined as scheduled.

Clinical Protocol for Dental Exams and Treatment:

1. Research staff will arrive at assigned site wearing face mask/covering. Staff will perform proper hand hygiene upon arrival.
2. Equipment will be set up in work areas. Once equipment is set up, it will be disinfected and appropriate barriers will be placed
    a. Equipment includes dental chair, operator chair, compression unit, tray/light, assistant tray, sharps container, equipment supply locker
    b. Disinfection procedure includes spraying equipment with Cavicide and allow to sit for three(3) minutes, then wipe with Caviwipes and allow to dry
3. Once research staff has taken the participant's temperature and determined that they passed the COVID-19 Screening Questionnaire, the dentist will review the health history before the participant is moved to the exam/treatment area
4. The participant will wear their mask until seated in the dental chair and the clinical team is ready to perform the dental exam. There will be no physical contact permitted, such as shaking hands, etc. Access to the treatment area should be limited to appropriate staff and the participant only, when possible.
5. Paperwork in the treatment area should be limited as much as possible, placing new paperwork away from patient contact area when possible and stored on a clipboard, under a plastic sheet protector, which may be wiped with a disinfectant wipe. Pens are not to be shared among the research staff
6. Hygienists and dentist will don proper PPE
    a. Dentist/hygienist perform proper hand hygiene

b. Put on disposable gown, typing all ties or snapping all snaps, this may require help from another provider
c. Put on surgical mask
d. Put on face shield
e. Perform proper hand hygiene again
f. Put on gloves, pulling down over wrists of gown

7. Participant will be seated in dental chair and will remove mask when instructed. Hygienist will place patient napkin on participant. The hygienists will perform exam while the recorder charts. The dentist will check charting, confirming areas for treatment as trained.
    - If no active decay is detected, participant will be dismissed from treatment area to complete exit paperwork with research staff.
8. The hygienists perform treatment using all necessary precautions to reduce aerosols and contamination, such as high volume evacuation and cotton rolls
    - The treatment will be SDF or ART as determined by the treatment assignment of the housing site.
9. . Once treatment is complete, the dentist will check the areas of treatment
    - Photos may be taken of treatment area by research assistant
10. The hygienist will remove and dispose of the patient napkin and the participant will then don their personal mask and leave the treatment area
11. The examining hygienist and dentist will remove gloves, perform proper hand hygiene and sign necessary paperwork
    - Pens are not to be shared between staff
12. If gloves have been removed, hygienists will then perform proper hand hygiene and put on gloves. Hygienists will remove and dispose of all barriers in garbage, all instruments will be disposed of in red sharps container.
13. Hygienists will disinfect treatment area while wearing proper PPE
    a. Spray dental chair, operator chair, compression unit, tray/light, assistant tray, sharps container, equipment supply locker with cavicide
    b. allow to sit for three (3) minutes
    c. wipe with Caviwipes and allow to dry
14. Hygienists will remove gloves, perform proper hand hygiene and apply new barriers as trained, to prepare for next participant. Hygienists will spray face shield with soap/water solution and wipe dry with paper towel or clean face shield with alcohol pad
15. After completing treatment for the day, equipment will be disinfected and disassembled
    a. Spray dental chair, operator chair, compression unit, tray/light, assistant tray, sharps container, equipment supply locker with Cavicide
    b. allow to sit for three (3) minutes
    c. wipe with Caviwipes and allow to dry

d. Spray and wipe floors with prepared Lysol solution and allow to dry

16. Dentist/hygienists will then remove PPE
    a. Properly remove and discard gloves
    b. Remove and dispose of gown
    c. Perform hand hygiene
    d. Remove face shield and clean with soap/water solution and a paper towel or alcohol pads
    e. Remove surgical mask
    f. Perform hand hygiene
    g. All staff should don personal mask to exit the facility

***ALL PARTICIPANTS AND PROJECT STAFF WILL BE INSTRUCTED TO CONTACT RESEARCH PERSONNEL IF THEY EXPERINCE ANY OF THE SYMPTOMS AS ASSESSED BY THE COVID-19 SCREENING QUESTIONNAIRE/ADA COVID-19 EMPLOYEE SCREENING LOG/CWRU DAILY HEALTH ASSESSMENT, RECORD A TEMPERATURE >*100.0*, TEST POSTIVE FOR COVID-19 AND/OR LEARN THEY HAVE BEEN IN CONTACT WITH A PERSON WHO HAS TESTED POSTIVE FOR COVID-19 WITHIN 2 WEEKS OR 14 DAYS OF THEIR DENTAL EXAM/RECRUITMENT INTERVIEW OR WORK DAY.

Once the COVID-19 pandemic ends, we will follow the original proposed plan for all visits.

7.1 **Baseline Visit (T_0) (Day -30 to 14)**

Recruitment/Enrollment

Study staff will recruit potential participants at the 22 participating housing facilities in coordination with the housing service coordinators and by using an in person approach at venues scheduled at the housing facility.

- Service coordinators will be provided with an introductory letter/flyer containing study information to be given to tenants and to be posted in public areas of the facility and will arrange an informational meeting for tenants (study dentist will give a talk on the interventions as suggested by our stakeholders).

- Service coordinators will arrange in-person recruitment meetings for study staff to present information regarding the study at scheduled group events (e.g. tenant meetings, health fairs, study informational presentations). For planning purposes, service coordinators will have a sign-up sheet for those interested in the sessions. At the conclusion of the session, study staff will meet individually with those interested to:

    - Review inclusion/exclusion criteria to determine eligibility (**Refer to Sections 5.1, 5.2**) utilizing the Screening and Eligibility Form

    - Obtain informed consent by reviewing the written consent form (Refer to Section 15.3) with the potential participant; ensuring comprehension of the study and

procedures, answering any questions, signing the consent form acknowledging that informed consent was reviewed and obtaining subject signature acknowledging consent was obtained. Consent will be obtained one time prior to the initiation of any study activities and will remain in effect for the duration of the study.

One-On-One Data Collection Interview

Study staff will interview participants at the housing facility to obtain contact and socio-demographic information and enter participant responses to the Participant Questionnaire which includes medical history, oral health behavior, oral health symptoms, tooth pain/sensitivity, and oral health quality of life.

Baseline Dental Exam

- Dentists will administer the Safety Questionnaire (Pre-Exam).
- Hygienists will perform initial dental exam examination at participant's respective housing facility to determine eligibility to continue in the clinical trial based on caries status.
- Study staff will record results of dental exam examination.
- Hygienists, under the direction of the study dentist, will proceed as follows:
- If the participant has an urgent cavity or another serious dental problem, they will be instructed to go for dental care immediately and their participation will end.
- If the participant has no cavities or other urgent problems, they will be instructed to continue regular visits with their dentist and their participation will end.
- If the participant has cavities that require treatment but no urgent problems, they will receive one of two treatments at this visit and will continue to participate in the research. Hygienists will administer the intervention treatment (based on study arm) to all untreated active root or coronal carious lesion with ICDAS-II lesion severity code of 3 or greater.
- If a participant reports any issue with the applied treatment within one week of the treatment date, the study team will return to the housing facility to examine and correct the treated tooth as needed. Within 48 hours, the study team will call the participant to ask the participant if the issue has been resolved and will administer a paper safety questionnaire. The completed paper safety questionnaire will be stored in the CRF folder and documentation of the return visit/treatment will be added to the participant's electronic record.

Follow-Up Data Collection

- Study staff will contact participants who received treatment by phone (within 48 hours of treatment) to complete the safety survey.

7.2 26-Week Visit (T_{26}) (Day 168 to Day 196)

Dental Exam and Treatment

- Dentists will administer the Safety Questionnaire (Pre-Exam).

- Hygienists will perform dental examination at participant's respective housing facility to evaluate caries arrest and identify new decay.
- Study staff will record results of dental examination.
- Hygienists, under the direction of the study dentist, will administer the intervention treatment (based on study arm) for all previously treated lesions and newly identified active root or coronal carious lesion with ICDAS-II lesion severity code of 3 or greater.
- Study staff will give participants referral sheets with exam results and direction to follow up with their personal dentist for routine dental care.
    - If a participant reports any issue with the applied treatment within one week of the treatment date, the study team will return to the housing facility to examine and correct the treated tooth as needed. Within 48 hours, the study team will call the participant to ask the participant if the issue has been resolved and will administer a paper safety questionnaire. The completed paper safety questionnaire will be stored in the CRF folder and documentation of the return visit/treatment will be added to the participant's electronic record.

Follow-Up Data Collection

- Study staff will contact participants by phone (within 48 hours of treatment) to complete the safety survey.
- Study staff will interview participants one-on-one at the housing facility to update contact information and enter participant responses to the oral health symptoms, tooth pain/sensitivity, and oral health quality of life and satisfaction surveys.
- Study staff will randomly select 24-30 participants who have completed treatment for three focus group sessions to be held at a housing facility during years two and three. Participants will be selected from those who have completed treatment and is geared to understanding participant experiences with non-surgical regimens and to identify ways to improve and disseminate in other community-based settings nationally.

7.3 52-Week Visit (T_{52}) (Day *365* to 379)

Dental Exam and Treatment

- Dentists *or hygienists* will administer the Safety Questionnaire (Pre-Exam).
- Hygienists will perform dental examination at participant's respective housing facility to evaluate caries arrest and new decay.
- Study staff will record results of dental examination.
- Study staff will give participants referral sheets with exam results and direction to follow up with their personal dentist for further treatment or routine dental care.

Follow-Up Data Collection

- Study staff will contact participants by phone (within 48 hours of treatment) to complete the safety survey.
- Study staff will interview participants one-on-one at the housing facility to update contact information and enter participant responses to the oral health symptoms, tooth pain/sensitivity, oral health quality of life*, COVID-19 dental visit* and the satisfaction survey.
- Study staff will randomly select 24-30 participants who have completed treatment for three focus group sessions to be held at a housing facility during years two, t*hree and four.* Participants will be selected from those who have completed treatment and is geared to understanding participant experiences with non-surgical regimens and to identify ways to improve and disseminate in other community-based settings nationally.

7.4 Withdrawal Visit

The following procedures will be followed for participants who choose to withdraw early or whose participation is terminated by the PI:

- Personal contact (by phone or in-person) by study staff will be made to confirm withdrawal.
- Record any adverse event reported by participant.
- Debrief about the interventions.
- Obtain responses to the study questionnaires (if applicable)
- If a participant withdraws or moves from the housing facility, visits and data collection will end with these participants being considered lost to follow-up. Data collected up to the point of withdrawal will be used for analysis.

7.5 Unscheduled Visit

Unscheduled visits for participants may occur if an enrolled individual could not complete a scheduled study procedure during the timeframe study staff is scheduled to be on-site at the housing facility. In these cases, every attempt will be made by study staff to complete the dental screening/exam/treatment and/or data collection interview as near to the visit window as possible. Study data would be collected per protocol guidelines, but the time length between visits will be accounted for in the analysis stage if necessary.

8 STUDY PROCEDURES /EVALUATIONS

8.1 Study Procedures/Evaluations (IR-4)

Study procedures include interventions and survey/questionnaire performed to assess the primary outcome, secondary outcomes, and moderators. The intervention is based on study arm. Study Participants in Arm 1 receive silver diamine fluoride (SDF) while Arm 2 participants receive atraumatic restorative treatment (ART) and fluoride varnish (FV). There will also be a process evaluations (Safety, Satisfaction) at each of the interventions applied. See Table 8.1.1 for more details on the measure, sources, and timeline. The study timeline is as follows: Baseline visit (T_0) (visual / tactile dental screening exam / 1st intervention), 26-week visit (T_{26}) (visual / tactile dental screening exam / 2nd intervention), and 52-week visit (T_{26}) (visual/tactile dental screening exam).

Table 8.1.1 Quantitative Summary of measures, sources, and timeline (IR-4)

Variable Type	Measure	Scale	Source	Timeline
Intervention by Study Arms	● Biannual SDF (Arm 1) ● ART + biannual FV(Arm 2)			T_0, T_{26}
Primary Outcome	*Clinical dental exam* ● Caries arrest	● % freq of arrested surface/teeth ● overall score	● ICDAS Coronal and Root [Dikmen 2015][44]	T_0, T_{26}, T_{52}

	Self-reported evaluation ● Tooth pain/sensitivity	● overall score	● PROMIS v.1.0 - Pain Intensity 3a [Modified for Dental][45] ● Dental Discomfort Questionnaire [Modified for Adults from Versloot et al. 2006][46]	T_0, T_{26}, T_{52}
Secondary Outcomes	*Clinical dental exam* ● New decay *Self-reported evaluation* ● OH-quality of life	● # freq of new decay teeth ● GOHRQoL overall score	● ICDAS Coronal and Root [Dikmen 2015][44] ● Geriatric Oral Health Quality of Life (GOHRQoL) [Atchison and Dolan, 1990][47]	T_0, T_{26}, T_{52} T_0, T_{26}, T_{52}
Process Outcome	● Safety ● Satisfaction	● % freq. adverse event ● overall score ● overall score	● Safety Questionnaire (Pre- and Post-Exam/Treatment [Adapted for Adults from Milgrom et al. 2018][48] ● Treatment Satisfaction Questionnaire for Medication (TSQM) [Modified for Dental][49] ● Satisfaction with New Treatment for cavities [Modified for Adults from Crystal et al. 2017][50]	T_0, T_{26}, T_{52} T_{52} T_{52}
Moderators	● Socio-demographic	● % freq.	● NHANES III [CDC, 1988][51]	T_0

	● Medical Condition	● % freq.	● Common Chronic Heath Condition for Adults 65+ [Adapted from NCOA 2017][52]	
	● Oral Health Behavior	● overall score	● Oral Hygiene [Adapted from Kuusela 1997, WHO survey 1997][53,54]	T_0
	● Oral Health Symptoms	● overall score	● Self-Reported Measures of Current Oral Disease/Tissue Damage [Adapted from Gilbert et. al 1997][55]	T_0
				T_0

Pre-T_0 = Prior to baseline

T_0 = 0-week / Baseline visit / Baseline visual / tactile dental exam (Arm 1: SDF, Arm 2: ART + FV)

T_{26} = 26-week follow-up visit / Visual / tactile dental exam (Arm 1, Arm 2)

T_{52} = 52-week final visit / Visual / tactile dental exam (Final)

8.1.1 Quantitative outcomes of interventions

The primary (i.e., carries arrest, tooth pain / sensitivity) and secondary outcomes (i.e., presence of new decay, oral health-related quality of life) measure the effectiveness of the study interventions. The process outcome are to access the safety of the interventions and to ascertain patient satisfaction with the treatment 1 year after the initial treatment.

Primary outcome: **Older adults caries arrest and tooth pain / sensitivity (Arm 1: SDF vs. Arm 2: ART + FV) will be assessed through:**

- Clinical dental exam: will be performed at the two intervention time points (T_0, T_{26}) and final time point (T_{52}) by a trained and calibrated dental hygienist according to the International Caries Detection and Assessment System II (ICDAS-II).[44] The exam will be used to identify a change in oral health status between the Baseline visit and the 26-week visit (T_0 and T_{26}) as well as the 26-week visit and the 52-week visit (T_{26} and T_{52}).

- Self-reported evaluation: Scales on tooth pain / sensitivity (PROMIS v.1.0, Health Organization[56]; Dental Discomfort Questionnaire (DDQ)[46]) will be used to measure levels of change in oral pain / sensitivity improvement. Higher scores on the PROMIS and DDQ

indicate increased tooth pain / sensitivity. These measures will be conducted during the baseline visit, 26-week visit, and 52-week visit (T_0, T_{26}, and T_{52}).

Secondary outcomes: Older adults' new decay and GOHRQoL (Arm 1: SDF vs. Arm 2: ART +FV) will be assessed through:

- Clinical dental exam: A newly carious tooth is defined as any tooth receiving an ICDAS lesion code ≥3 that received a sound code on the previous dental exam or any tooth surface with an ICDAS filling code ≥3 that previously did not have one. The number of teeth with new decay or filling will be assessed through clinical dental exams (T_0, T_{26}, and T_{52}) and recorded on the ICDAS Assessment form.

- Self-reported evaluation: The Geriatric Oral Health-related Quality of Life (GOHRQoL) [47] consist of 12 questions and will be used to assess the impact of the intervention on participants overall oral health quality of life. The overall score will be calculated with higher scores indicating that the participant has greater oral health Quality of Life. The measures will be collected within two week of the baseline visit, the 26-week visit (T_0, T_{26}), and 52-week visit exam (T_{52}).

Process outcome: Safety and satisfaction and moderating variables (Arm 1: SDF vs. Arm 2: ART +FV) will be assessed through:

- The Safety Questionnaire-Revised for Adults[48] consists of 15 main adverse events (i.e., existence of dental insurance, severity of adverse symptoms after receiving the dental treatment) and will be used to identify adverse events. Participants will complete this survey pre- and post-exam/treatment at the baseline visit, 26-week visit, and the 52-week visit, respectively. The treatment satisfaction will be assessed through the treatment satisfaction questionnaire for medication[49] (TSQM) modified for Dental and satisfaction with new treatment for cavities, [50] comprised of six questions. The overall average score will be assessed from these two scales with higher mean score indicating better satisfaction with the study treatment. The measures will be conducted during the baseline visit, follow-up visit, and final exam (T_0, T_{26}, and T_{52}).

Moderating Variables will be assessed only at Baseline (T_0) through:

Moderating variables will be collected using the following instruments: a 9-item socio-demographic questionnaire (NHANES III, CDC)[51], a 10-item common chronic health condition for adults 65+ questionnaire (adapted from the Nation Council on Aging(NCOA)[12], a 12-item self-reported measures of current oral disease / tissue damage questionnaire (Gilbert et al., 1997)[55], and a 5-item oral hygiene (adapted from Kuusela, 1997 and WHO) [53,54] These measures will be considered as potential moderators and will be collected at the baseline visit only.

Table 8.1.2. Qualitative Focus Study Procedures / Evaluations (to be conducted in year 2, *year 3, and year 4 either virtually or at a convenient housing facility, based on housing site circumstances at the time of focus group scheduling)*

Subject	Planning / Design	At the Focus Group Process	Data Collection
Group Participants	**Recruitment** ● Participants who will complete the clinical trial randomly invited to one of the three focus group interviews	**Comfortable environment** ● Provide signed and dated consent form at the beginning of interview protocol	**Activities** ● Generate ideas / efforts to contribution ● Engagement and input on focus group activity
Moderator	**Design for group interview** ● Develop an agenda and discussion guide ● Review participants' demographics and characteristics ● Finalize / review a protocol design with the study staff	**Probing with Semi-structured questionnaire** ● Opening ● Introduction ● Transition ● Key questions ● Conclude (Breen, 2007)[57] **Data collection** ● Audio recording ● Summary notes	**Key topics** ● Inquire as to participants' levels of **satisfaction** in accessibility and practices of a received intervention (Robinson et al., 2005)[58] ● **Dissemination** of the treatment of SDF or ART+FV to other older populations ● **Barriers** experienced in getting treatment of SDF or ART + FV (Newton et al., 2001)[59] ● **Resources and challenges** in seeking dental care (adapted from Gussy et al., 2006)[60]
Study Staff	**Define methodologies** ● Define a purpose and goal	**Process** ● Observational notes	**Data Analysis** ● Transcription of audio tapes

	● Scheduling meeting ● Guidelines for recruiting (non-proportional approach) ● Book a room for an interview ● Arrange materials (name tags, chairs, and table)	● Capture of non-verbal activities **Acknowledgment** ● Refreshments ● Gift card ($25) / travel cost	● Data coding / organizing information by using Atlas.ti software

8.1.2 Focus Group Study Procedures / Evaluations

Focus groups will be led by an experienced moderator trained in qualitative interviewing techniques. The moderator will use a semi-structured interview guide to gather a large number of opinions and engage in a collective brainstorming of ideas and solutions.

Focus group discussions are a part of qualitative technique wherein a researcher assembles a group of individuals to discuss a specific topic that can provide a deeper understanding of or insight into a particular issue.[61] We will use the phenomenological approach and ground theory to focus group research for the current study.

Recruitment, planning and development of the discussion guide

- *Participant recruitment* will occur prior to the focus group meeting. The research team will contact individual participants to promote participation for the focus group study via phone, e-mail, and in-person. We will randomly invite participants that have successfully completed the clinical trial until 30 participants from the 22 housing facilities agree to participate in one three focus group discussion (non-proportional sampling).

- *The moderator* will prepare a focus group guide for each discussion. The moderator will outline the flow of questions and topics to be covered. This discussion strategy will encourage participants to pursue topics of interest and to reveal experiences regarding the treatment.

- *The research staff* will develop and agree on standard practice for focus group discussion. In collaboration with the moderator, the research team will establish management guidelines for the focus group meeting that enable the moderator to effectively capture key phrase and understand group dynamics. The staff will reserve a convenient and accessible venue and prepare necessary materials for interview. Arrangements will be made for name tags, food, and drinks for participants. An honorarium ($25) will be given to each participant in appreciation of their time as well as any travel costs.

Focus group procedures and data collection

The focus groups will be conducted either virtually or at a convenient housing facility, based on housing site circumstances at the time of focus group. Each focus group participant will have provided a signed and dated consent form prior to the beginning of the group discussion. The moderator will encourage active participation in interviews to gain valuable inputs and ideas.

- *The moderator* will be responsible for initiating the discussion and keeping the group on task as well as creating a comfortable, relaxed atmosphere. Focus group sessions will be approximately 90 minutes and an audio recording will be also made so as to ensure a complete record of what was discussed.
- *The moderator* will conduct each focus group using a semi-structured interview guide based on five categories of questions (opening, introduction, transition, key, and ending). The interview guide for participants will focus on levels of satisfaction of the treatment (SDF or ART + FV) in terms of accessibility and convenient practices; barriers and facilitators experienced while receiving treatment procedures of SDF or ART +FV; resources and challenges of the treatment of SDF or ART + FV; a potential in dissemination of the treatment of SDF or ART + FV to other populations of older adults. The interview discussion will be audio-recorded, and this data will foster an in-depth understanding of participants' perceptions and attitudes toward the conducted interventions.
- One or two *staff members* who have been trained in focus group interviews will attend the discussion to record non-verbal cues, signals, and facial expressions. Observational notes during the interview and summary notes after the interview will also be recorded by the study staff. After each focus group, in discussion with the moderator, the study staff will debrief on key concepts and identify any new questions that should be added to the next focus group, if needed. Focus group data collected with two approaches of a group interview and observational approaches will be transcribed into data coding steps. The coded data will be analyzed using Atlas.ti software, which helps to integrate interview findings into coherent qualitative study results.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

This study involves administration of two FDA approved devices, which are applied using approved standardized protocols for administration (SDF, ART+FV).

9.1.1 Unanticipated Problems

Unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The primary responsibility for the evaluation of unanticipated problems lies with the PI of the protocol. This includes the documentation, investigation, and follow-up of these events. Consistent with CWRU IRB policy, the PI will report these events to the IRB within three (3) business days of discovery of the problem or event.

The PI must complete the Unanticipated Problems, Deviations, Adverse Events Form and submit it to the IRB. If the Unanticipated Problem does not meet these criteria, then the event does not meet reporting criteria and should be retained in the investigator's file for reference.

9.1.2 Adverse Events

An adverse event (AE) is any unintended negative experience associated with the study materials or research procedures. Adverse events include both physical and psychological harms.

9.1.3 Serious Adverse Events

A serious adverse event (SAE) is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment

9.2 Time Period and Frequency for Event Assessment and Follow-Up

The primary responsibility for the evaluation of these events lies with the PI of the protocol. This includes the documentation, investigation, and follow-up of these events. For those events that require reports to the IRB, it is the PI's responsibility to submit the reports in a timely manner. If new risks to the participants are identified they must be included in a revised consent form.

Multiple factors determine if an Unanticipated Problems, Deviations, Adverse Events Form is required. One of the most important distinctions is whether the event is expected or unexpected. To make this determination, it is necessary to know the underlying condition of the subject including co-morbidities, and the severity and frequency of events in participants who qualify for the study. An expected adverse event meets one or more of the following criteria:

- Attributed to the underlying condition of the participant being studied.
- Attributed to the subject population being studied.
- Identified in the literature, investigator brochure, other risk documentation or informed consent.

An unexpected adverse event meets one or more of the following criteria:

- Not listed in the informed consent, protocol, or other study documents.
- Not attributed to the underlying condition of the subject taking into account co-morbid conditions.
- Not attributed to the subject population
- Severity and/or frequency of the event are beyond the range previously known.

Unanticipated problems will be recorded in the data collection system throughout the study.

Study staff will *administer the Safety Questionnaire (Pre-exam) prior to the dental exam and treatment and then* contact each participant by phone 24-72 hours following treatment receipt to administer the Safety Questionnaire by phone. The PI, and co-investigator, Dr. Chao, will review

all records of participants who indicate they needed medical care or experienced symptoms since the treatment on a weekly basis to determine the severity and its relation to the treatment. Proper notifications will then be made to the IRB, PCORI and the DSMB based on their evaluation. Events will be followed for outcome information until resolution or stabilization. The PI will record all reportable events though the duration of the study.

The PI must complete the Unanticipated Problems, Deviations, Adverse Events Form and submit it to the IRB. If the Unanticipated Problem does not meet these criteria, then the event does not meet reporting criteria and should be retained in the investigator'

9.3 Characteristics of an Adverse Event

9.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

9.3.2 Expectedness of SAEs

We do not anticipate any serious adverse events related to the study intervention. The Study PI and co-investigator Dr. Chao will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

9.3.3 Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL

3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

9.4 Reporting Procedures

9.4.1 Unanticipated Problem Reporting to IRB and PCORI

Incidents or events that meet the criteria listed above for unanticipated problems require the creation and completion of an unanticipated problem report form. The following information will be included when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- All unexpected problems involving risks to subject or others must be reported to the Case Western Reserve IRB within three (3) calendar days of discovery of the problem or event. The only exception to the above timeframe is for the reporting of deaths. All internal, unexpected, study-related deaths must be reported to the IRB as soon as the investigator learns of the event. Reporting to PCORI must also occur within 7 calendar days if death or a life-threatening event occurs or within 14 calendar days for all other SAEs.

For all reporting periods "days" refers to business days after the PI learned of the event. All reportable events need to be reported to the IRB within the timeline even if the information about the event is incomplete. Further information can be added with a follow-up report. All adverse events, including those reported to the study team must be promptly reviewed by the PI and any event that changes the risk/benefit ratio of the study, or requires a change in the protocol or the consent form, must be reported to the IRB within 3 business days.

- The PI and the study team must make the protocol changes as soon as possible and submit the revised documents to the IRB via the Amendment form
- Other events reported to CWRU IRB are as follows:
- All fatal events must be reported to the IRB as soon as the PI learns of the event, if the PI believes the event to be related to the study. If the death is determined to be unrelated to the study, it must be reported at the time of next Continuing Review.
- Deaths which occur after the subject's research participation has ended do not need to be reported to the IRB unless the death is related to study participation.
- All serious adverse events must be reported as soon as the PI learns of the event.

- All non-serious events and summary reports are kept in the PI's files and do not need to be reported to the IRB. The IRB does not require the PI to report adverse events that occur to subjects enrolled in an observational study or non-interventional study unless the event is related to study participation, causes a change in study design or increases risk for other participants.
- If a CWRU PI is notified about an event that occurred at another site in a study related to, but not the same as, the CWRU protocol, and the event results in a change in the protocol, consent form, or the risk/benefit ratio, the adverse event must be reported within 3 business days of learning of the event.
- If the change in the CWRU protocol is due to publication of results from another study which has an adverse impact on the CWRU protocol, it should be reported as soon as the PI learns of the valid publication.
- The PI who conducts research projects funded by a federal agency is obligated to report adverse events that are serious and unanticipated simultaneously to both the federal agency and to the IRB. The IRB has a separate and distinct obligation to report the adverse events to government authorities
- If the event changes the risk for other study participants and requires changes in the consent documents, report as soon as the PI learns of the event (but within 3 business days).
- Adverse events which occur in another study (including fatal events) and which do not result in a change in the protocol, consent form, or the risk/benefit ratio for the study, do not need to be reported to the IRB but should be kept on file by the PI.

9.4.2 Serious Adverse Event Reporting to PCORI

Any AE meeting the specified Serious Adverse Event criteria will be submitted on an SAE form to PCORI within 7 days. This report may be sent by fax or email. This process applies to both initial and follow-up SAE reports.

The PI will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

- All study-related deaths and immediately life-threatening events will be recorded on the Serious Adverse Event Form and submitted to Product Safety within 7 calendar days of site awareness.

- Study-related serious adverse events other than death and immediately life-threatening events, will be reported by fax within 14 calendar days of site awareness.

All SAEs will be followed until resolution or stabilization.

9.5 Halting Rules

It is not anticipated that there is a necessity for halting rules as the proposed study treatments are considered safe and approved by the FDA. But, all safety and adverse events data will be reviewed by the DSMB members. DSMB will review the interim analysis of the safety data and will give their recommendations every year.

10 STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of members with appropriate clinical, statistical, scientific, and ethical expertise. PCORI will not appoint the Board as per their guidelines. But the study investigators would be responsible for the appointment of the DSMB. The DSMB will meet at least annually to assess safety and effectiveness data, study progress, and data integrity for the study. If concerns arise, more frequent meetings may be held. The DSMB will operate under the general rules of a NIH -approved charter that will be approved at the organizational meeting of the DSMB. The DSMB will provide recommendations to the study investigators and PCORI.

In addition to the PI's responsibility for oversight, study oversight will be under the direction of PCORI. The PI will submit a report every 6 months to the PCORI for review. This report will include data regarding enrollment and retention, unanticipated problems and protocol deviations, outcome measures, quality management findings and other relevant parameters. If necessary, additional steps may be taken to ensure data integrity and protocol compliance.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

This study tests the hypothesis that simple medical treatment (Arm 1) is non-inferior to typical dental treatment (Arm 2) for primary outcomes (caries arrest, tooth pain/hypersensitivity) and secondary outcomes (new decay, oral health quality of life) at 12-months post treatment.

11.2 Sample Size Considerations (RC-3)

For continuous outcomes we computed power using a variance correction (i.e., variance inflation factor) to take into account possible correlations of outcomes within cluster. All computations of required effective samples sizes (or corresponding power) were done using the PASS 2005 software. For binary outcomes, we used a specialized program for cluster randomization (a non-inferiority test comparing two proportions).

The primary outcome tooth pain was defined as change in pain (based on a 100-mm visual analogue pain scale (VAS), where higher is worse pain) from baseline to 1 year. We assume a mean difference of 0 between SDF and ART+FV, and consider non-inferiority to be within a margin (mean difference) of 8 between SDF and ART+FV arms; and based on prior literature also assume a common standard deviation of 25.[62] Further, we assumed an average of 25 subjects recruited per site, an intraclass correlation (ICC) of 0.01 (based on prior studies and literature),[63,64] and a 15% dropout rate (based on prior studies). The use of a 0.025 alpha-level one-sided t-test to test the null hypothesis of inferiority versus the alternative hypothesis of non-inferiority (as defined above), 11 sites per treatment group (corresponding to 275 subjects per treatment group or 550 total) will provide an estimated 89% power to conclude non-inferiority. Even if the ICC is higher (0.02), there will still be 83% power to detect non-inferiority.

A second primary outcome is arrest rate. Previous data[2,65] show a high arrest rate (of around 90%) for ART + FV. We expect a similar arrest rate for SDF.[34] For the power calculation we suppose the unit of analysis to be the person, and consider the binary outcome of 'arrest' defined as all lesions for an individual being arrested. We assume equal (person-level) arrest rates of 90% for the ART+FV and SDF groups, and consider non-inferiority to be within a margin (difference in arrest proportions for ART+FV versus SDF) of 0.09. With the same assumptions as before using a 0.025 alpha level one-sided z test, the targeted sample size of 275 subjects in 11 sites per treatment group will provide an estimated 85% power to conclude non-inferiority. For a higher ICC of 0.02, there will still about 80% power to detect non-inferiority.

11.3 Planned Interim Analyses

The safety data will be analyzed periodically for review by the DSMB. Safety Review

11.3.1 Efficacy Review

N/A

11.4 Final Analysis Plan (IR-1, RC-4)

Each primary outcome will be compared between the SDF and ART+FV groups. For tooth pain, a 95% confidence interval (CI) based on a t-test for the difference in mean responses (SDF minus ART+FV) will be computed. If this confidence interval lies within the interval (-∞, 8) we may conclude 'non-inferiority' of SDF relative to ART+FV treatment. The confidence interval may secondarily be examined to assess possible superiority of one intervention over the other. For arrest rate, a 95% CI for the difference in rates (based on a z statistic) will be computed. If this confidence interval lies within the interval (-0.09, 1) we may conclude 'non-inferiority' of the SDF relative to ART+FV treatment. As above, possible superiority of one intervention over the other may also be assessed. For other outcomes, we will also compute 95% CI for differences in means (or proportions for binary outcomes). These secondary outcomes will be assessed in an exploratory manner for possibly superiority or inferiority based on appropriate margins.

We will seek to corroborate initial results using a generalized estimating equations (GEE) approach. For each outcome we will fit a GEE (marginal) model that includes a treatment indicator and prognostic variables (including sociodemographic variables, medical conditions, and oral health behaviors). Appropriate link functions (e.g., logit link for binary outcomes and identity link for continuous outcomes) will be specified and an exchangeable working correlation matrix used to allow for correlations within site. The arrest outcome will be analyzed as a binary outcome (as described in the sample size section), and secondarily as the number of arrested lesions assuming an appropriate distribution (e.g., negative binomial) and link function (e.g., log link). Robust t tests with correction for a small number of clusters[66] will be used to test for treatment effects and corresponding 95% confidence intervals computed.

Secondarily, we will extend the above GEE approach to analyze the repeated (baseline, 26 and 52-week) measures for each outcome. The models for each outcome will include the same prognostic variables as before, as well as time and a time by treatment interaction. We will allow for correlations among the repeated measures, e.g., using a first-order autocorrelation structure. If a substantial within-facility correlation is found we may need to incorporate facility as a second cluster levels (within which person – the first cluster level – is nested). We will estimate and test (via a robust t-test) the interaction term to compare trends over time for the two interventions. If the use of two cluster levels is not found to be feasible in the GEE approach, we will consider a generalized mixed effects model approach.

Causal Inference standards **(CI-1, CI-2, CI-3, CI-4)**: Our use of randomization and adjustment in regression models should be sufficient to provide causally interpretable intervention effect estimates; special causal inference techniques such as propensity score or instrumental variable methods often indicated for observational studies, will therefore not be necessary for our data analysis. We will avoid biases in causal inferences about the intended interventions by using an intent-to-treat approach, in which individuals are analyzed according to randomized groups without regard to (extent of) treatment actually received.

Sensitivity Analyses **IR-5)**: We will check sensitivity of conclusions to model assumptions as well as methodological decisions such as outcome definition. In particular, for the arrest outcome, our primary analysis is based on a binary indicator of 'complete' arrest of all lesions for an individual. We will seek to corroborate results from this approach with an alternative approach analyzing

number of lesions arrested. For the GEE analyses, planned for all outcomes, sensitivity will be assessed in part by using alternative working covariance structures and alternative sets of predictors. For some outcomes, alternative distributions will be considered; for example, for number of arrested lesions, possible distributions include Poisson, negative binomial, zero-inflated Poisson (ZIP), and zero-inflated negative binomial (ZINB). Sensitivity to assumptions regarding missing data will also be investigated as described further below.

Missing Data. *(a) Methods to prevent and monitor missing data **(MD-1, IR-7)***: All questionnaires (using tablets) and dental assessment forms (using paper), will be managed in an electronic database (REDCap) by study staff. Weekly quality control checks will be run for outliers, entry errors, missing data, and potential data anomalies. Statistical analyses, summary and missing data reports will be generated by the study biostatistician (Dr. Albert) monthly during the study. *(b) Statistical Methods to Handle Missing Data and Account for Statistical Uncertainty Due to Missingness **(MD-2):*** The primary analyses, which use GEE based on all available observations, assume outcomes are missing completely at random (MCAR). As an initial assessment of missing data patterns, intervention groups (including by relevant subgroups and time point) will be compared with regard to missing outcome rates. We wlll test for a relationship between missingness and outcomes at early time points to evaluate the plausibility of the MCAR assumption. We will use multiple imputation methods (an established method) to help assure valid inferences. *(d) Plans to Record and Report Dropout and Missing Data **(MD-3, IR-7)**:* The trial data will be managed using REDCap software, currently running at Case Western Reserve University (CWRU). REDCap[67] is a secure web-based application providing an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures, and automated export procedures for seamless data downloads to common statistical packages. Missing data reports will be generated weekly from REDCap for timely resolution and reporting purposes. *(e) Plans to Examine Sensitivity of Inferences to Missing Data Methods **(MD-4)**:* As noted above, multiple imputation will be used to obtain valid inferences in the presence of data that are not missing completely at random. We will use predictive mean matching with an appropriate prediction model depending on the outcome (e.g. logistic regression for binary outcomes, linear regression for continuous and count outcomes). Alternative imputation models will be used as part of sensitivity analyses.

Heterogeneity of Treatment Effects **(HTE: HT-1, HT-2, HT-3)**. Our primary hypothesis addresses the effect of interventions at 12 months, as well as the longitudinal effect of the interventions. There is no empiric data on comparative effectiveness of these interventions, but individually they have similar effectiveness from prior literature. In particular, we will assess the possible moderators indicated in Figure 1; specific examples include age (e.g., dichotomized as age < 75 versus age >= 75), presence of two or more medical conditions, gender, and race. Heterogeneity of treatment effect will be assessed by adding to the GEE models each potential moderator, along with the corresponding interaction with treatment. We will test moderator by treatment interactions to determine evidence for subgroup differences in the treatment effect. Corresponding 95% confidence intervals for the treatment effect for each subgroup will be computed. Secondarily, we will conduct an interaction tree approach such as CHAID (Chi-squared automatic interaction detection) an extension of CART (Classification and Regression Trees)[68] to simultaneously assess the set of potential moderators, and determine subgroups that have significant intervention effects.

Reporting Plan **(IR-5)**: To allow for assessment of study's internal and external validity, we will adhere to standard reporting guidelines for randomized clinical trials as specified by: EQUATOR network;[69] SPIRIT 2013 statement;[70] and CONSORT 2010 statement.[71]

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. CWRU will permit authorized representatives of PCORI, and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

All records with identifiable information will be kept in secured locked storage units or stored in secure online databases. Only local (i.e. study staff) at CWRU and PCORI staff appointed to the trial will have access to the records. Access by the PCORI staff is for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Specific original documents and data records include, but are not limited to:

- **Participant Consent chart** contains all participant-identifying information. The chart includes the signed consent form, Consent Documentation form, the Contact Info form, Unanticipated Problem or Serious Adverse Event forms, Telephone Contact log and Reimbursement form. These documents will contain the participant's name and other confidential information (i.e. names of family members). (Electronic and Paper Based)

- **Participant Research chart** includes Case Report Forms (CRFs) and the Progress Notes Checklist. Examples are: ICDAS caries dental assessment form ; and Participant Questionnaire (Electronic and Paper Based). Medical information for chronic illnesses will be from participant self-report.

- **Tracking logs (in RedCap)** (Electronic)

- **Memoranda** (paper-based)

Some case report forms will be completed by study staff (Research Assistants, the Research Associate, or Project Coordinator, depending on the event). Exceptions will be the Participant Questionnaires, Contact information and Consent form(s) that will be completed by the Participant. The study staff will complete all provider audit forms. Data will be handled in accordance with GCP, U.S. federal regulations, local regulations (if applicable), and instructions from PCORI. All essential documents should be filled out completely and signed by the study staff collecting or recording the data. When necessary, essential documents (like consent/assent forms) will be reviewed, signed and dated by the principal investigators or study staff designated by the principal investigators.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Definitions

Quality Assurance (QA)

The process to ensure the quality of the intervention meets the study design expectations.

Quality Control (QC)

A set of routine technical activities to measure and control the quality of the intervention and accuracy of data acquisition as the intervention is being implemented.

13.2 Study Intervention and Study Questionnaires

13.2.1 Quality Assurance Procedures

Study Staff:

Study staff who will recruit and interact with participants at the facilities, and document study activities will attend in-person training which will incorporate the topics of human subject protection, Good Clinical Practice (GCP), and adherence to the study protocol. As part of tracking and managing study records, staff members will learn how to document activities that occur with subjects, update study documentation and use the tracking and audit logs. To assess proficiency, the study staff will be certified in the topics presented to ensure their comprehension of the expectations.

In addition, all study staff will be trained to make calls during the dedicated staff training. A script for each type of call will be created in REDCap and study staff will practice during training until they are proficient in utilizing the script and recording the call details.

Additionally, the dental hygienists will undergo calibration exercises prior to the main study to become proficient in exam related study procedures and to maintain intra- and inter-examiner agreement. Dentist experts in the application of SDF, ART, and FV will train and calibrate the dental hygienist and study dentist in the clinical protocol during a two day training session. Additionally, a gold standard examiner will calibrate/train the examiners in the ICDAS protocol in a separate 4-day training session. Detailed clinical and caries assessment training, calibration and reproducibility protocols are in the attached training protocol. Hygienists will not utilize dental radiographs. At the 26-week and 52-week exams, the hygienists will not have access to the results of the baseline examination to avoid detection bias.

Data Manager:

Before formal data entry begins, appropriate study staff will be trained on a custom-configured, study-specific Electronic Data Capture (EDC) test system by the data manager. This procedure is for data entry training and user acceptance testing, concurrently. After completing didactic training, staff trainees will enter pre-specified test data into the test EDC system, including invalid data, to provide additional training and familiarity with the data entry process. Their

entered data will be compared against the pre-specified test data. After completion of training, staff members will be granted permission to use the EDC production environment for collection of project data.

13.2.2 Quality Control Procedures

Study Staff:

Data quality control is primarily conducted at the study team level through internal processes of data review/data monitoring as the data is collected and through periodic custom reports (See Table 16.4.1). Dental exam data will be reviewed for accuracy and completeness after each study visit by the Dental Hygienist. The Study Staff will review the questionnaires after the participants have completed them. Each paper form and questionnaire will be entered and verified by two separate individuals. Forms completed electronically via tablets will be checked by study staff prior to leaving the facility. Any field that is unclear will be clarified with the participant who completed the document.

All study forms and questionnaires collected and entered into the database will be checked for inconsistencies and range and assessed for missing data. Any inconsistencies, outliers, or missing data observed will be compared to the paper document and appropriate corrective actions carried out. REDCap's native data resolution workflow will be used to document and fix any data anomalies. The Data Manager will also respond to data queries generated by the PI, Study Coordinator, or other study staff.

Data Manager:

The Data Manager will design custom reports. Utilization of an EDC system, such as REDCap, means that automated data checks can be implemented within the data entry system. This helps to prevent most errors immediately. The automated checks are also supported by an extensive system of custom reports and manual validation procedures that help to assist in the resolution of any additional errors.

The Data Manager will create a standalone Data Validation Plan (DVP). The DVP will describe in more specific detail the edit-checks that will be performed within the EDC system and the SOPs for data entry and quality management. The Data Manager together with the study team, will be responsible for the creation, testing, and finalization of the DVP for the project.

Following collection of all data from a project, additional data processing will be required by the Data manager, e.g., longitudinal coding of dental examination data, creation of psychosocial scale scores. In conjunction with that data processing, The Data Manager will run regular validation reports to detect data anomalies and will work with the project staff to resolve any data anomalies that arise during data entry. Following PI concurrence, the database will be locked.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

14.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Case Western Reserve University (FWA#: 00004428) IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the research record.

14.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, representatives for Case Western Reserve University, and the representatives of the study sponsor (PCORI).

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

An authorized PCORI member may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

All information about the participant will be kept strictly confidential and be used only for study purposes. When study results are published or presented, all information will be presented in group form, without identifiable information.

15 DATA MANAGEMENT PLAN

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

15.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the Study Staff, Data Manager and Study Coordinator under the supervision of the PI. All source documents must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the PI.

15.2 Data Collection Methods and Organization of the Data

15.2.1 Data Collection Methods

Data for this study will be captured using dental exams, forms, questionnaires, and audio recordings. Study data will be collected and stored using the REDCap Electronic Data Capture (EDC) platform hosted by Case Western Reserve University. REDCap is a secure, web-based application designed to support remote data capture for research studies, providing: 1) an intuitive interface for validated data entry, 2) audit trails for tracking data manipulation and export procedures, 3) automated export procedures for seamless data downloads to common statistical packages, and 4) procedures for importing data from external sources.

15.2.2 Setting up the EDC

Electronic data capture forms will be created to match paper CRFs. Before the project begins recruitment a test/non-production environment will be created where the study form will be created and tested. Once the forms have been approved by either the PI and/or the study coordinator they will be moved to the production environment. Real study data will only be entered in the production environment.

Prior to being released for data collection, CRFs are configured by the Data Manager in non-Production REDCap test environments for user acceptance testing. Each form and the overall database will be tested by the Project Coordinator and Study Staff. The user acceptance test includes exercises involving data entry for a complete mock subject from start to finish, including interviews conducted with interruptions (terminated early and restarted). Items that have been tested and approved by the PI and/or Study Coordinator are then migrated to the Production environment. Items that will be configured in the non-production environment and then migrated to the production environment are as follows:

Study Forms: Confirms that they have been properly translated from the paper CFRs and are free from errors in content, design and formatting.

Univariate and valid value checks: Confirm that checks have been properly imported from specifications document. Manually test each check.

Multivariate and cross-checks: Confirm each check via test data designed to trigger a query.

Custom functions: e.g. custom reports. Confirm that each custom report is functioning with test data designed to trigger an event. Second programmer code review, if possible.

Generation of subject numbers: Confirm that participant IDs are generated according to specifications.

Customized form or variable delivery (e.g. dynamic fields): Confirm against schedule of events and against other specifications. We will use standard operating procedures (SOPs).

Data completion guidelines: Confirm that the completion guidelines are properly associated with each form/field. This will be achieved using SOPs and training manuals for specific roles such as Data Manager, Study Staff, etc.

Derived variable computation: Confirm against specifications using test data.

Role assignment: Review system. Confirm using list of role functionality. Have testers assigned to each role and ensure that they are only able to do/see what they are entitled to, per their assigned role.

Data Extracts: Review extracted data and ensure that it matches specifications (e.g., annotated CRF)

System Reports: Review EDC reports and ensure they are functioning according to expectations. Run reports on test data.

REDCap automatically outputs both a data dictionary and metadata on the data structure once the forms are designed. If the forms are modified REDCap automatically updates the data dictionary and metadata to reflect the changes. The data dictionary and metadata will reside in Redcap.

15.2.3 Changes to a Production EDC System

The goal is to minimize changes made to the data management plan once the protocol-specific configuration is loaded into the Production server and is 'live.' Absolutely necessary changes will be required to go through the same process as in the initial EDC system. The changes will first be entered into the EDC system test environment and tested by the Data Manager. The new changes will then go through user training and acceptance testing in the Test environment prior to implementation in the REDCap Production environment. Finally, when the Study Coordinator and/or PI deems the changes are ready to be implemented in the Production environment, the changes will be implemented in the REDCap Production environment.

When the changes have been implemented in the REDCap Production environment, all appropriate training will be conducted to ensure the Project Staff understands the changes in their work going forward. Documentation of all changes and testing will be stored in on the CWRU local network drive and will be versioned using the version control scheme outlined below.

15.2.4 Version Control for Study Forms

Study Forms will be versioned and named in the file according to the following file naming convention. Each change in version will be tracked on a version tracking log, which will be stored on the School of Dental Medicines local network drive and will be accessible to all study personnel.

The rules for file naming are below…

1. The first element of the file name should be the date. Use YYMMDD format for date. This format makes sure all of your files stay in chronological order, even over the span of many years.

2. Special characters such as ~ ! @ # $ % ^ & * ( ) ` ; < > ? , [ ] { } ' " and | should be avoided.

3. When using a sequential numbering system, using leading zeros for clarity and to make sure files sort in sequential order.

4. For example, use "001, 002, ...010, 011 ... 100, 101, etc." instead of "1, 2, ...10, 11 ... 100, 101, etc."

5. Do not use spaces. Some software will not recognize file names with spaces, and file names with spaces must be enclosed in quotes when using the command line. Other options include

   - Underscores, e.g. file_name.xxx

   - Dashes, e.g. file-name.xxx

   - No separation, e.g. filename.xxx

   -Camel case, where the first letter of each section of text is capitalized, e.g. FileName.xxx

6. Version number should be the last element in the name and should start with 0.1 for the first draft of a document. The first IRB approved version of a document should be version 1.0.

15.2.5 Organization of Paper Form

Study forms may be completed by participants on paper, and subsequently entered into REDCap by study staff, or on a tablet directly into REDCap. Paper forms will be securely stored in a locked file cabinet. Recorded audio will be deleted from the digital recording device immediately after being stored on a secure CWRU School of Dental Medicine network drive.

15.3 Types of Data Collected

Participant data for this study will include: (1) dental exam data, (2) study questionnaires and (3) intervention tracking data. Additionally, audio recordings will be used for fidelity monitoring. A summary of the types of data collected, the storage location and the methods of completion can be seen in Figure 15.3.1.

Figure 15.3.1

Mail Clinical Trial

Storage Location	Form/ Questionnaire	Type	Method of Completion
Consent Folder and REDCap	Consent Form	Consent	▪ Direct Entry by Participant and study staff into RedCap via Tablet ▪ Paper Form
Consent Folder and REDCap	Consent Documentation	Consent	▪ Direct Entry by study Staff into RedCap ▪ Paper Form
Consent Folder and REDCap	Participant Contact Form	Contact	▪ Direct Entry by Participant into RedCap ▪ Paper Form
CRF Folder and REDCap	Screening and Eligibility Form	Screening and Eligibility	▪ Direct Entry by study Staff into RedCap ▪ Paper Form
CRF Folder and REDCap	Participant Questionnaire A	Demographics, Medical History, Oral Behavior and Oral Health Symptoms	▪ Direct Entry by Participant and study staff into RedCap ▪ Paper Form
CRF Folder and REDCap	Participant Questionnaire B	Tooth Pain/Sensitivity and Oral Health Quality of Life	▪ Direct Entry by Participant and study staff into RedCap ▪ Paper Form
CRF Folder and REDCap	Safety Questionnaire (Pre-Exam) and Participant Questionnaire C	Safety	▪ Direct Entry by study staff into RedCap ▪ Paper Form
CRF Folder and REDCap	Participant Questionnaire D	Satisfaction	▪ Direct Entry by study staff into RedCap ▪ Paper Form
CRF Folder and REDCap	Intervention Delivery Tracking	Treatment Log	▪ Direct Entry by study staff into RedCap ▪ Paper Form

CRF Folder and REDCap	Dental Exam Forms	Oral Health Screening and Carries Arrest and New Decay	▪ Direct Entry by study staff into RedCap ▪ Paper Form
Focus Groups			
CWRU Dental School Network Drive	Focus Group Transcriptions and Recordings	Treatment Satisfaction	▪ Digital Recording and Electronic Transcription Files

15.4 Methods to Prevent and Monitor Missing Data.

Utilization of an EDC system, such as REDCap, means that automated data checks can be implemented within the data entry system. This helps to prevent most errors, immediately. The automated checks are also supported by an extensive system of custom reports and manual validation procedures that assist in the resolution of any additional errors.

At the data collection stage, study staff will also make sure at the visit that all forms are checked for completeness of paper and electronic data.

15.4.1 Univariate Alerts

Value Alerts for Multiple-choice Fields (allowing selection of only 1 option)

• The user is required to choose only one out of a series that represents different response option choices. Such multiple-choice fields are defined as radio buttons or are displayed in a dropdown menu of choices.

Valid Value Alerts for Multiple-choice Fields (allowing selection of more than 1)

• The user is required to choose at least one and is allowed to choose all options from a series that represents different data choices. This type of multiple-choice field is defined as a checkbox.

Valid Value Alerts for Number Fields

• The user is required to enter a number in a format as indicated in the completion guideline and notes provided by the system or the system will not allow data entry.

• The system does not allow entering any character that fails the specification (e.g., letters in a number field).

Valid Value Alerts for Missing Data

• To ensure completeness, even in the case that data are not available, options of refused, don’t know or not-applicable may be made available.

15.4.2 Multivariate and Cross-module Alerts

- Confirming that "Other, specify:" is completed when "Other' is marked.
- Confirming that only valid options are selected in a "choose all that apply" multiple choice field, where the range of options deemed valid depends on some other parameter.
- Confirming data of part-fields which are references for system-based calculations when calculated values are out of indicated range (e.g., BMI calculation based on weight and height).
- Comparing the dates and times of all assessment time points to confirm that they occur in an appropriate sequence. For example, a Study Week 1 assessment should occur before a Study week 3 assessment.

15.5 Schedule and Content of Reports

Quality control is primarily conducted at the study team level through internal processes of data review/data monitoring using periodic custom reports. See Table 16.4.1 for the project-specific custom reports for the main trial.

Table 15.4.1 Project-specific custom reports

Responsible for Addressing	Name of Report	Frequency
CWRU	Weekly Enrollment	Weekly during recruitment
CWRU	Cumulative Enrollment	Weekly during recruitment
CWRU	Informed Consent & Documentation Errors	Weekly during recruitment
CWRU	Participant Questionnaire Completion	As Required by CWRU
CWRU	Dental Exam Completion	As Required by CWRU
CWRU	Intervention Completion Log	As Required by CWRU
CWRU	Safety Data	Weekly during intervention delivery
CWRU	26-week and 52-week to be scheduled	As Required by CWRU

The Data Manager will run regular validation reports to detect data anomalies and will work with the project staff to resolve any data anomalies that arise during data entry. REDCap's native

data resolution workflow will be used to document and fix any data anomalies. The Data Manager will also respond to data queries generated by the PI, Study Coordinator, or other study staff.

At the completion of the study, the study Biostatistician will conduct analyses of the data and assist in preparation of study publications and presentations. The Data Manager will provide technical and data support for the Biostatistician throughout the study.

The Data Manager will generate regular reports showing enrollment and potential data anomalies, which will be sent to PIs, Project Coordinators, and other relevant study staff Data Manager will generate a monthly enrollment report (or as requested by the DSMB or PCORI Program Official) for sharing progress of the study (see table 15.4 above).

15.6 Data Storage and Preservation plan

Overview of Data Storage and Security in REDCap

REDCap servers are hosted at CWRU and are guarded by multiple firewall and intrusion detection systems. All electronic connections to the REDCap environment are encrypted. The REDCap production system is comprised of a web server front-end and a MySQL database server back-end. The MySQL server back-end resides in the protected CWRU server subnet that is protected by CWRU-maintained firewalls. Only CWRU Information Technology system administrators are authorized to access the back-end database server directly.

Processes of sanitization, filtering, data type checking, and escaping all help to protect against methods of attack, such as Cross-Site Scripting (XSS) and SQL Injection. To specifically protect against Cross-Site Request Forgery (CSRF), which is another method of attack, REDCap utilizes a “nonce” (a secret, user-specific token) on every web form used in the application. The nonce is generated as a unique value for each new REDCap session. Additionally, REDCap employs “rate limiting” on its web pages, in which there is a set maximum number of web requests per minute that are allowed from a single IP address, and after that maximum is hit, the IP address of that user is permanently banned from REDCap.

REDCap implements authentication to validate the identity of end-users that log in to the system. For security reasons, the password in the database table is not stored as plain text but as an encrypted one-way hash of the password.

Disaster Recovery Plan

REDCap databases are backed up on a regularly scheduled basis.

• The backup cycle consists of daily incremental backups and full back up each week. The backups are stored on a local storage disk environment. The local backup files are stored for 14 days and then automatically aged off of the system.

• Additionally, all of the backup files are copied, using dedicated network connections, to a remote storage disk environment. Remote backup files are kept for 30 days and then aged off of the system.

• System and file restorations are conducted daily as a part of routine daily operations. Test restores are conducted at the request of the application owner and are based on the specific application requirements.

Overview of Data Storage and Security for Paper File

Paper files with be stored at CWRU in locked offices inside of locked cabinets. Only the Data Manager and the PI will have access to the keys for the locked cabinets. The consent charts and the CRF charts will be stored in different rooms to help separate data from identifying information. A linking file will be keep electronically in REDCap and on a secured network drive at CWRU School of dental medicine. This network drive has been specifically designated to store PHI. Furthermore, access to each folder is restricted by the owner and will be update to limit access to only current study personnel.

15.7 Study Records Retention

Study documents should be retained for 7 years after the final report is submitted to PCORI in accordance with PCORI's policy on data management and sharing. These documents may be retained for a longer period, however, if required by local regulations or CWRU IRB.

16 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical study protocol or Good Clinical Practice requirements. The noncompliance may be on the part of the subject, the investigator, or study staff (e.g., Project Coordinators, Study Staff). As a result of deviations, corrective actions are to be developed by the PI and/or Project Coordinator, and implemented promptly.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1
- Noncompliance, Sections 5.20.1 and 5.20.2.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to PCORI and the Case Western Reserve IRB, according to their requirements as outlined below

According to CWRUIRB, Major Deviations are reported to the IRB within 14 calendar days of discovery. Minor Deviations are kept in the investigator's file to be reported at the time of continuing review.

Examples of Major Deviations:

- Failure to obtain informed consent, i.e., there is not documentation of informed consent or informed consent was obtained after initiation of study procedures;
- Informed consent obtained by someone not approved to obtain consent for the protocol;
- Use of invalid consent form, i.e. consent form without IRB approval; or outdated/expired consent form;
- Enrollment of a participant who was ineligible for the study;
- Performing a research procedure not in the approved protocol;
- Failure to report serious adverse event to IRB; sponsor; and/or regulatory agencies;
- Failure to follow the approved study protocol that affect participant safety or data integrity (e.g., study visit missed or conducted outside of required timeframe, or failure to perform a laboratory test);
- Failure to follow safety monitoring plan;
- Continuing research activities after IRB approval has expired;
- Use of recruitment procedures that have not been approved by the IRB;
- Enrolling significantly more subjects than proposed in the IRB protocol;
  Examples of Minor Deviations

- Missing original signed and dated consent form (only a photocopy available);
- Missing pages of executed consent form;
- Failure to follow the approved study protocol that does not affect participant safety (e.g., study procedure conducted out of sequence, failure to perform a required test, missing laboratory results, study visit conducted outside of required timeframe.).

17 PUBLICATION

17.1 Policy on Public Access

This study will comply with the *PCORI's Policy on Public Access*, which ensures that the public has access to the published results of PCORI funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from PCORI funds to the digital archive PubMed Central upon acceptance for publication.

Awardees with published, peer-reviewed articles resulting from PCORI-funded research must ensure that the articles are made available in PubMed Central in accordance with the following conditions:

- Awardees are to ensure that an electronic copy of their final peer-reviewed manuscript is deposited in PubMed Central within four weeks of its acceptance for journal publication. (Instructions for posting are *available here*.)

- The manuscript is to be made publicly available in PubMed Central no later than 12 months after the official date of journal publication.

In addition, PCORI support must be acknowledged in every article reporting findings from research funded in whole or part by PCORI, consistent with PCORI Guidelines. The acknowledgement statement must include the applicable PCORI contract number, which will enable PCORI to link the published outputs of PCORI-funded research to the support PCORI has provided.

PCORI will expect all awardees to comply with this Policy on Public Access.

18 DATA SHARING PLAN

18.1 Data Deposition and Data Availability

The Full Data Package will be maintained at CWRU for a period of at least seven (7) years following acceptance by PCORI of the Final Research Report. During this period, PCORI may notify PI of PCORI's intent to provide funds for the deposition of the Full Data Package to a PCORI-designated repository. Reasons for such notification may include PCORI's estimation of high importance of and interest in research project findings, request(s) from external researchers for data access, or the PI's expressed interest in sharing the data.

Regarding the data sharing plan, we endorse and will follow the NIH guidelines available at http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm. We will work in a collaborative manner with PCORI in all aspects of the proposed project including sharing all materials (protocol, questionnaire/survey etc.), data, and results that will be developed and produced through this proposed project. All research resources including the Manual of Procedures (MOP), study manuals, questionnaire/survey will be made available to the public.

Sharing Data and Research Materials

For any external investigators requesting data, user agreements need to be executed as per Institutional guidance and in accordance with IRB regulation. These agreements also forbid the external investigator from passing along the data to a third party. Investigator requests should clearly state the goals of their study and what specific data is requested.

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APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

APPENDIX A: SCHEDULE OF EVENTS

Measure/Process	Type	Instrument/Evaluation/Procedure	Timeline (Study Week)						
			-2	0	2	26	28	52	54
Screening and Eligibility Form	Screening and Eligibility	Screening and Eligibility Form	X						
Consent Form	Consent	Case IRB Template	X						
Consent Doc.	Consent	Case IRB Template	X						
Contact Form	Contact	Contact Information Form	X			X			
Participant Questionnaire A	Demographics	Demographics [Adapted from NHANES III][72]	X						
Participant Questionnaire A	Medical History	Common Chronic Heath Condition for Adults 65+ [Adapted from NCOA 2017][52]	X						
Participant Questionnaire A	Oral Behavior	Oral Hygiene [Adapted from Kuusela 1997, WHO survey 1997][53,54]	X						
Participant Questionnaire A	Oral Health Symptoms	Self-Reported Measures of Current Oral Disease/Tissue Damage [Adapted from Gilbert et. al 1997][55]	X						
Participant Questionnaire B	Tooth Pain/Sensitivity	PROMIS v.1.0 - Pain Intensity 3a [Modified for Dental][45]	X				X		X
Participant Questionnaire B	Tooth Pain/Sensitivity	Dental Discomfort Questionnaire [Modified for Adults from Versloot et al. 2006][46]	X				X		X
Participant Questionnaire B	Oral Health Quality of Life	Geriatric Oral Health Quality of Life [Atchison and Dolan, 1990][47]	X				X		X
Participant Questionnaire C	Safety	Safety Questionnaire [Adapted for Adults from Milgrom et al. 2018][48]			X		X		X
Participant Questionnaire D	Satisfaction	Treatment Satisfaction Questionnaire for Medication (TSQM) [Modified for Dental][49]							X
Participant Questionnaire D	Satisfaction	Satisfaction with New Treatment for cavities [Modified for Adults from Crystal et al. 2017][50]							X

Measure/Process	Type	Instrument/Evaluation/Procedure	Timeline (Study Week)						
			-2	0	2	26	28	52	54
Intervention Delivery	Treatment	SDF or Art + FV Based on Study Arm		X		X			
Intervention and Visit Tracking			X	X	X	X	X	X	X
Safety Questionnaire (Pre-Exam)	Safety	Safety Questionnaire [Adapted for Adults from Milgrom et al. 2018][48]		X		X		X	
Dental Exam Form	Oral Health Screening	Oral Health Screening and Referral Form		X		X		X	
Dental Exam Form	Oral Health Screening	Visual Examination to Detect Gingival or Soft Tissue Stomatitis or Ulcerative Lesions [Adapted from Milgrom et al. 2018][48]			X		X	X	
Dental Exam Form	Carries Arrest and New Decay	ICDAS Coronal and Root [Dikmen 2015][44]		X		X		X	