TITLE: THE BUILDING ADAPTIVE SCHOOL-BASED INTERVENTIONS FOR CARIES STUDY (BASICS): A PHASE III SEQUENTIAL, MULTIPLE ASSIGNMENT, RANDOMIZED TRIAL OF MINIMALLY INVASIVE THERAPIES TO REDUCE TREATMENT NONRESPONSE

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THE BUILDING ADAPTIVE SCHOOL-BASED INTERVENTIONS FOR CARIES STUDY (BASICS): A PHASE III SEQUENTIAL, MULTIPLE ASSIGNMENT, RANDOMIZED TRIAL OF MINIMALLY INVASIVE THERAPIES TO REDUCE TREATMENT NONRESPONSE

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NYULH Study Number:	s24-01908
Funding Sponsor:	National Institutes of Health 9000 Rockville Pike, Bethesda, MD 20892 Phone: (301) 496-4000
Study Product:	1. Silver Diamine Fluoride (SDF) 2. PreviDent Fluoride Varnish 3. FluoroDose Fluoride Varnish 4. Resin-Modified Glass Ionomer (RMGI)
ClinicalTrials.gov Number	Not yet assigned

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Amended: [date]
Amended: [date]

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States
SDF	Silver diamine fluoride
FV	Fluoride varnish
ART	Atraumatic restorative treatment
GIC	Glass Ionomer Cement
SMART	Sequential multiple assignment randomized trial
SMART	Silver modified atraumatic restorative treatment
AI	Adaptive interventions
DTR	Dynamic treatment regime

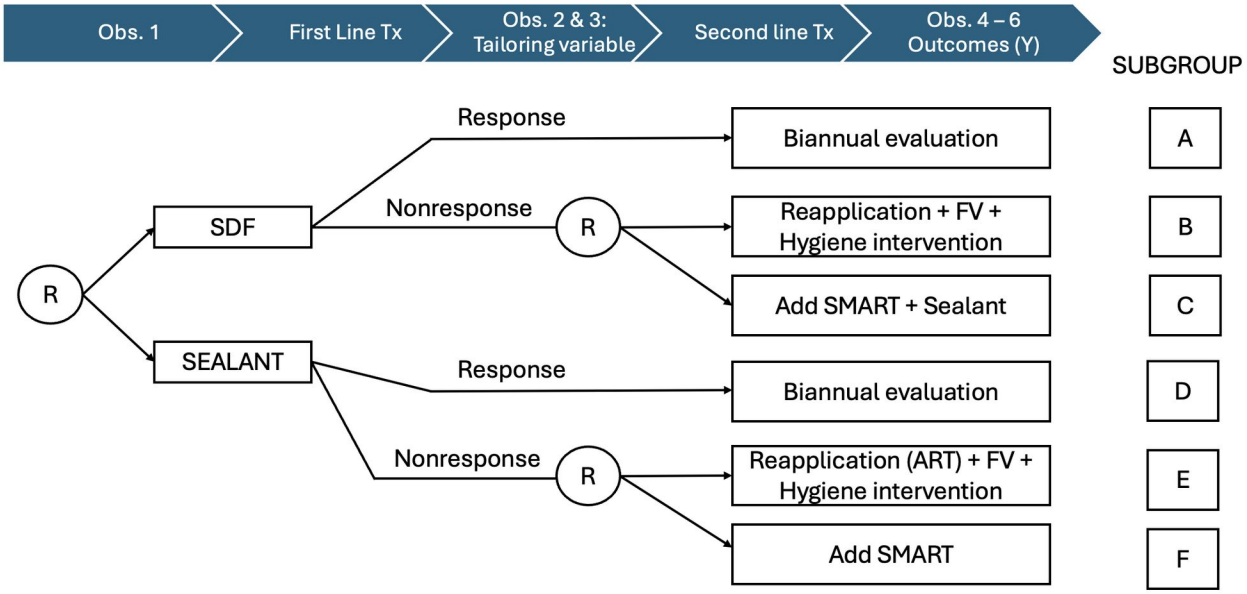
SBCP	School-based caries prevention
SBDP	School-based dental program
SBSP	School-based sealant program
SBHC	School-based health center
IPW	Inverse probability weighting
MSM	Marginal structural models
GLMM	Generalized linear mixed models
BASICS	Building Adaptive School-based Interventions for Caries Study
NIMHD	National Institute on Minority Health and Health Disparities
SYS	Schoolyard Smiles

Protocol Summary

Title	The Building Adaptive School-based Interventions for Caries Study (BASICS): A phase III sequential, multiple assignment, randomized trial of minimally invasive therapies to reduce treatment nonresponse
Short Title	BASICS
Brief Summary	School-based caries prevention (SBCP) programs increase access to essential oral healthcare and reduce dental caries, the world's most prevalent noncommunicable disease. However, approximately 1 in 4 children participating in SBCP fail to respond to care, remaining at risk for persistent caries and associated sequelae. The Building Adaptive School-based Interventions for Caries Study (BASICS) is a sequential, multiple assignment, randomized trial of minimally invasive interventions to reduce treatment nonresponse in school caries prevention. BASICS will be conducted in an estimated 1200 children in grades K-3 who are participating in an existing school-based caries prevention program. The SBCP program – known as SCHOOLYARD SMILES (SYS) – is providing all treatments to be tested in the study as part of their standard program procedures. For the study, the sequence of treatments being provided will be altered, with the goal of improving treatment effectiveness and efficiency. Parents or guardians of children who are participating in the SBCP program will consent to participate in the BASICS study, and children will provide assent. Study participants will then be randomly assigned to an initial intervention, after which their treatment responsiveness will be measured and subsequent randomization pathways assigned, resulting in six treatment subgroups forming different adaptive preventive interventions (AI), also known as dynamic treatment regimes (DTR). The study will collect data biannually
Phase	Phase 3
Objectives	1. What is the most effective first-stage treatment for caries prevention, assessed via caries incidence? 2. What is the most effective sequence of treatments to reduce treatment nonresponse, assessed via caries incidence? 3. What is the optimal dynamic treatment regime given patient attributes, assessed via varies incidence modified by disease severity, sociodemographics, and treatment history? 4. Given alternative strategies, what is the most cost-efficient allocation of resources that can most significantly affect population health, measured by time and cost of care?
Methodology	Sequential, Multiple-Assignment, Randomized Trial (SMART)
Endpoint	The primary study endpoint is treatment nonresponse, defined as presence/absence of caries and the total number of caries observed.
Study Duration	Five years

Participant Duration	2.5 years
Duration of IP administration	Five years
Population	Our targeted enrollment is 1200 children aged 5-12 years. From prior studies, we anticipate an equal sex allocation, and average age of 7.2 years, predominantly from low-income families. The general health status of the population is healthy.
Study Sites	Schools participating in the Schoolyard Smiles SBCP
Number of participants	1200
Description of Study Agent/Procedure	Treatments include silver diamine fluoride (SDF), fluoride varnish (FV), and resin-modified glass ionomer cement (GIC) sealants to prevent caries. SDF is also provided to arrest caries. GIC can also be used to arrest caries, and when used for this purpose, is called atraumatic restoration, or ART. SDF and ART can also be provided in combination, which is referred to as silver modified atraumatic restorative technique (SMART). We will also provide participants with an electronic toothbrush. For interventions using SDF, one drop (0.05 ml) of SDF solution at 38% concentration (2.24 F-ion mg/dose) will be dispensed per child. Posterior tooth surfaces to be treated will be dried, and the SDF will be applied with a microbrush to all asymptomatic cavitated lesions and to all pits/fissures on bicuspids and molar teeth for 30 s. For interventions using sealants and/or ART, glass ionomer sealants will be applied to all pits and fissures of bicuspids and molars, and placement of ART on all frank asymptomatic cavitated lesions. For Silver Modified Atraumatic Restorative Technique, SDF will be applied as described above on any carious tissue, followed by glass ionomer cement for restoration. Auto-cure GIC will be used to reduce SDF/sealant stain. For FV, a 5% NaF solution will be applied to all teeth after application of SDF or ART.
Reference Therapy	As a sequential, multiple-assignment, randomized trial, there is no reference therapy beyond standard of care (dental sealants), as described above.
Key Procedures	Full-mouth visual-tactile oral examination, SDF application, FV application, dental sealant application.
Statistical Analysis	For objective 1, we will use generalized linear mixed models followed by marginal causal excursion effect estimation. For objective 2, we will use augmented inverse probability weighting (AIPW) with marginal structural models (MSM) and Q-learning. For objective 3, we will use microcosting in tandem with time studies.

Schematic of Study Design



Observation and Treatment Schedule

Observation	Procedures	Estimated Time
0-months (Time 1)	Initial treatment, SDF or sealant	Fall 2026
6-months (Time 2)	Tailoring observation, second line treatment	Spring 2027
12-months (Time 3)	Tailoring observation, second line treatment	Fall 2027
18-months (Time 4)	Outcome Observation	Spring 2028
24-months (Time 5)	Outcome Observation	Fall 2028
30-months (Time 6)	Outcome Observation	Spring 2029

Subgroup Size and Interventions

Subgroup A	N = 420	Silver diamine fluoride (single application)
Subgroup B	N = 90	Silver diamine fluoride (initial treatment) followed by SDF reapplication plus FV plus electronic toothbrushing
Subgroup C	N = 90	Silver diamine fluoride (initial treatment) followed by GIC sealant application and silver modified atraumatic restorations
Subgroup D	N = 420	GIC sealants (single application)
Subgroup E	N = 90	GIC sealants (reapplication, as ART) followed by FV plus electronic toothbrushing
Subgroup F	N = 90	Add SDF as silver modified atraumatic restorative treatment

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

As the world's most prominent noncommunicable disease [1], dental caries experience affects over 70% of children in the United States [2, 3]. A known determinant of caries is a lack of access to preventive and therapeutic care [4], resulting in disproportionate burdens of disease in low-income and minority children [2, 3]. Persistent untreated dental caries in children can lead to pulpal involvement, dental abscess, oral pain, and systemic infection [5, 6], and the effects of dental caries are not limited to dental and craniofacial health. Prior evidence shows that poor oral health is negatively associated with school attendance and academic achievement [7], with some estimates attributing up to thirty million hours of lost seat time per year due to dental issues [8], and those with untreated disease face negative impacts on oral health-related quality of life and psychosocial functioning.

School-based approaches for caries prevention, such as school sealant programs, are clinically and cost-effective interventions [9] and the Association of State and Territorial Dental Directors (ASTDD) reports that over 65% of states in the US have active school sealant programs [10]. Similarly, school fluoride initiatives can prevent caries

in permanent teeth [11] and are particularly effective in areas without community water fluoridation [12], and more comprehensive programs providing sealants, fluoride varnish, and atraumatic restorations can control existing caries and reduce their further incidence [13]. Silver diamine fluoride has also emerged as a promising addition to the school dental program portfolio, controlling existing caries and preventing new decay when applied along with fluoride varnish [14].

Despite this overall effectiveness, it is consistently observed that approximately 1 in 4 children participating in school caries prevention fails to respond to care, subsequently presenting with recurrence or first incidence of caries. For example, an open prospective cohort of children receiving comprehensive prevention showed that 20% of children consistently developed caries regardless of whether they were disease free or not at baseline [13], while data from school-based pragmatic trials observed that 24% to 36% of children receiving silver diamine fluoride (SDF) or glass ionomer sealants developed new caries sometime after receiving care [15, 16]. Prior etiologic studies of this treatment nonresponse to select preventive interventions demonstrated that there are innate microbial and environmental factors that may be related to the responsiveness to school-based care. In children receiving SDF, the salivary microbiome showed that separate clusters of bacterial species were enriched or depleted in responders compared to nonresponders [17], and machine learning models suggest that Prevotella pallens and Veillonella dentocariosa, as well as diet and hygiene behavior, may be useful in predicting nonresponse [18].

Chairside solutions are needed as an interventional strategy to mitigate treatment nonresponse in school-based caries prevention. The Building Adaptive School-based Interventions for Caries Study (BASICS) will develop and test dynamic treatment regimes (DTR) for patient nonresponse [19], incorporating elements of precision medicine into school caries prevention [20]. As a pragmatic trial, BASICS will be implemented in collaboration with an existing school-based caries prevention program (SBCP), known as SCHOOLYARD SMILES (SYS). SYS already provides the listed interventions to be studied in BASICS, but the order of receipt will change according to the experimental design. Following completion of the study, de-identified data from SBCP/BASICS participants will be provided to investigators for analysis.

In this protocol, the SBCP and SYS will be referred to interchangeably.

2.2 Name and Description of the Investigational Agent

This study involves the use of four agents for the prevention and management of dental caries: fluoride varnish (two formulations), silver diamine fluoride (SDF), and resin-modified glass ionomer (RMGI). All agents are standard-of-care interventions commonly used in school-based oral health programs. These products have American Dental Association (ADA) billing codes, are reimbursed by Medicaid and private insurers, and have been evaluated in multiple randomized controlled trials and systematic reviews demonstrating their effectiveness in caries prevention and management.

All four agents in this study—two fluoride varnish agents (PreviDent and FluoroDose), silver diamine fluoride (Advantage Arrest), and resin-modified glass ionomer (Fuji IX GP Extra)-- are FDA-cleared Class II medical devices. Additionally, all four qualify as Non-Significant Risk (NSR) devices, given their extensive history of use in dental practice and school-based oral health programs.

Three of the devise are used off-label: the two types of Fluoride Varnish (PreviDent and FluoroDose) and Silver Diamine Fluoride. The Resin-Modified Glass Ionomer is used on-label.

Off-label description: Fluoride varnish (PreviDent and Fluorodosh) and Silver Diamine Fluoride are approved for dental sensitivity and used off-label for the prevention and treatment of caries. This off-label use is supported by multiple federal and state organizations, including the American Dental Association.

Fluoride varnish and SDF are used in the United States and internationally for the prevention and treatment of caries.

Two fluoride varnish formulations will be used in this study:

PreviDent® Varnish

- **510(K) Number:** K132109
- **Classification Name:** Varnish, Cavity
- **Device Class:** 2
- **Manufacturer:** Colgate Oral Pharmaceuticals, 300 Park Avenue, New York, NY 10022
- **Indications for Use:** PreviDent Fluoride Varnish is a topical fluoride treatment for dentinal sensitivity.

Composition and Properties:

- 5% Sodium Fluoride (NaF) (22,600 ppm fluoride).
- Forms a protective film on the tooth surface, providing sustained fluoride exposure.
- Hardens on contact with saliva for easy application in school-based settings.

FDA Status and Regulatory Considerations:

- FDA-cleared medical device (Class II) under 510(k) pathway.

FluoroDose

- **510(K) Number:** K982915
- **Classification Name:** Varnish, Cavity
- **Device Class:** 2
- **Manufacturer:** Centrix, Inc., 770 River Road, Shelton, Connecticut 06484
- **Indications for Use:** FluoroDose Fluoride Varnish is a topical fluoride treatment for dentinal hypersensitivity.

Composition and Properties:

- 5% Sodium Fluoride (NaF) (22,600 ppm fluoride).
- Free from lactose, gluten, and nuts, it is safe for children with dietary restrictions.
- Quick application and strong adherence to the tooth surface make it ideal for school-based use.

FDA Status and Regulatory Considerations:

- FDA-cleared medical device (Class II) under 510(k) pathway.

Silver Diamine Fluoride (SDF)

- **Advantage Arrest (Silver Diamine Fluoride 38%)**
- **510(K) Number:** K102973
- **Classification Name:** Silver Dental Arrest
- **Device Class:** 2
- **Manufacturer:** Elevate Oral Care, 346 Pike Road, Suite 5, West Palm Beach, Florida 33411
  Indications for Use: SDF is used to treat dentinal hypersensitivity and arrest active caries lesions. The concentration of fluoride in SDF and fluoride varnish are indicated in the table below:

Fluoride product	Unit dose (ml)	Concentration (ppm)	F ion mg/ml	F ion mg/dose
SDF 38%	1 drop (0.05)	44,800	44.8	2.24
FV 5% NaF	0.25	22,600	22.6	5.65
	0.4	22,600	22.6	9.04
	0.5	22,600	22.6	11.3

Composition and Properties:

- Active ingredient: Aqueous Silver Diamine Fluoride (38.3% to 43.2% w/v).
- Inactive ingredients: Purified water, FD&C Blue 1.
- Arrests caries progression through a dual mechanism—silver ions act as an antimicrobial agent, while fluoride promotes remineralization.

FDA Status and Regulatory Considerations:

- FDA-cleared medical device (Class II) under 510(k) pathway.

Resin-Modified Glass Ionomer (RMGI)

- **GC America Fuji IX GP Extra**
- **510(K) Number:** K070319
- **Classification Name:** Tooth Shade Resin-Based Material
- **Device Class:** 2
- **Manufacturer:** GC America Inc., 3737 West 127th Street, Alsip, IL 60803
- **Indications for Use:** Fuji IX GP Extra is a resin-modified glass ionomer (RMGI) restorative material used for non-load-bearing restorations and caries stabilization in pediatric and high-risk populations.

Composition and Properties:

- Powder-liquid formulation composed of fluoro-alumino-silicate glass and polyacrylic acid.
- Fluoride-releasing material that provides long-term remineralization and chemical bonding to enamel and dentin.
- Strong, wear-resistant, and moisture-tolerant, making it ideal for atraumatic restorative treatment (ART) and interim therapeutic restorations (ITR).

FDA Status and Regulatory Considerations:

- FDA-cleared medical device (Class II) under 510(k) pathway.

2.2.1 Preclinical Data

The direct effects of SDF has received considerable study [12, 33, 34]: the mechanistic action of silver diamine fluoride includes reducing the growth of cariogenic bacteria through the antibacterial effect of silver, and also by promoting the remineralization of enamel and dentine caries [12]. Silver ions in SDF are thought to prevent bacterial aggregation through reaction with bacterial cellular surface proteins [35], harden soft carious lesions through reaction with phosphate or chloride ions resulting in the formation of silver salts (e.g., silver chloride), and increase the alkalinity of the environment through the formation of ammonium compounds hypothesized to have an acid-buffering effect.

The mechanism of fluoride varnish is the deposit of calcium fluoride on tooth surfaces, which is later converted through a remineralization reaction to fluorapatite [21]. In vitro studies of fluoride varnish demonstrate that applications of fluoride gel resulted in significant fluoride uptake in rats and cows, while human enamel application showed significantly greater fluoride uptake using a fluoride varnish. Other evidence showed that the use of fluoride varnish showed gains of more than 1000 wt-parts/10^6 at 1.5 um depth. Similarly, in vivo studies showed the crystalline nature of fluoride bones to be predominantly fluorapatite. After five weeks in vivo, teeth treated with FV had significantly greater fluoride concentration than control teeth [22].

ART using conventional glass polyalkenoate (ionomer) restorative cement (GIC) possesses fluoride-releasing properties, including bonding to enamel and dentine, as well as pulpal biocompatibility and ease of manipulation [23]. Prior studies show that fluoride released grom GIC makes tooth enamel and dentine more resistant to acidic invasion by bacteria, fluoride released grom GIC occur up to five years, and GIC acts as a fluoride reservoir, making teeth treated with ART less susceptible to caries for long periods of time [23, 24].

2.2.2 Clinical Data to Date

Dental sealants can significantly reduce the incidence of pit and fissure occlusal caries in primary and secondary molars and arrest the progression of noncavitated lesions [25, 26], leading to official clinical practice guidelines for their use by the American Dental Association [27]\. When compared to other caries prevention strategies, the cost-effectiveness of pit and fissure sealants [28] has led to their wide incorporation in pragmatic settings such as school-based sealant programs [9, 29].

A series of Cochrane Reviews show that topical fluorides are effective in the prevention of dental caries in primary and permanent teeth [30-33], and the effectiveness of topical fluoride is not dependent on baseline caries risk, caries severity, or external exposures to fluoride [34]. A national survey identified 40 school-based fluoride varnish programs, many of which are applied as part of a broader initiative, such as dental sealants on permanent dentition [35].

Atraumatic restorative treatment/interim therapeutic restorations (ART / ITR) and silver diamine fluoride (SDF) are noninvasive methods to prevent and arrest caries [36]. Silver diamine fluoride (SDF) is recommended by the American Academy of Pediatric Dentistry as a cost-effective approach for comprehensive caries management in children [37], and it has published guidelines for provision by primary care providers [38]. Reviews indicate that SDF reduces the risk of root carious lesions [39], is more effective than fluoride varnish [36], controls caries progression [40, 41], and is commonly used in community settings [42]. SDF is estimated to arrest anywhere from 47 to 90 percent of caries lesions after one application [14] and is considered to be a practical, affordable approach to community caries prevention, particularly in low socioeconomic areas [15]. It is also effective in the prevention of new caries [43]. When used as part of a school-based program, SDF has been shown to be comparable to dental sealants in the prevention [15] and control [16] of dental caries.

The average annual failure rate for single- and multiple-surface ART restorations in primary molars is estimated to be 5 and 17%, respectively [16], though this may be outperformed by conventional restorations [17]. Like SDF, prior studies of ART in community settings conclude that it is acceptable and effective in socioeconomically deprived groups [18]. More recently, a systematic review and meta-analysis of clinical outcomes of ART restorations in children estimated overall success rate of 71% and 67% after 12 and 24-months, respectively [44]. Operator error was a major contributing factor to the success of ART restorations [44].

2.2.3 Dose Rationale

All agents used in this study have been dosed according to the manufacturer's instructions, which are based on existing clinical evidence and regulatory approvals. These dosing regimens have been widely adopted in clinical practice and school-based oral health programs, ensuring both safety and efficacy in preventing and managing dental caries.

2.3 Rationale

Although existing evidence clearly shows the preventive and therapeutic benefits of silver diamine fluoride, fluoride varnish, and atraumatic restorations for the prevention and management of dental caries in school dental medicine programs, they are insufficient for a vulnerable subpopulation of high-risk children. We have previously showed that key bacterial species in the salivary microbiome, as well as hygiene behavior, are predictive of nonresponse. Our hypothesis is that adaptive preventive interventions can directly reduce nonresponse by incorporating precision medicine into school-based care. The described administration, dosage, and dosing regimens of study agents, as well as predefined interventional periods, are standard of care and based off existing clinical practice guidelines.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

All study procedures as described pose risks to subjects that are no greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. All agents included in this study are provided as part of routine clinical (preventive dental) care. Study procedures will not alter what is typically provided in any way that is expected to increase risk.

Participation in this study does not result in any added benefit for participants, as participants will still receive treatment provided by the school-based caries prevention program. Although all treatments provided in this study are the same as those provided in the SBCP program, potential risks from participation include receipt of treatment that may not be what would be originally prescribed by a dentist. This is due to randomization. These risks will be minimized as all children will receive complete care necessary for their oral health needs. No child will

be untreated. All children will receive treatments that are accepted and provided as standard of care in clinical practice.

The treatment-specific risk assessment for this study is based on the FDA-approved package inserts for silver diamine fluoride (SDF), fluoride varnish (PreviDent and FluoroDose), and resin-modified glass ionomer (GC America Fuji IX GP Extra). These products are widely used in clinical dentistry, and their risk profiles are well-documented in manufacturer guidelines and published literature. Additional risk information is drawn from the Investigator's Brochure (IB) for investigational applications and relevant published literature on the safety and efficacy of these dental interventions.

Established risk mitigation strategies for data security are in place to protect participants and are detailed below. The study follows strict data security measures and considers the special vulnerabilities of child participants. The value of the information gained will contribute to evidence-based improvements in school-based dental care programs.

1. **Silver Diamine Fluoride (SDF)**
    a. Immediate Risks:
        i. Allergic Reactions: Individuals with known silver allergies may experience localized hypersensitivity reactions.
            1. Mitigation: Participants with a known silver allergy will be excluded from the study.
        ii. Soft Tissue Irritation: Accidental application to gingival or mucosal tissues may result in temporary irritation, typically resolving within 3-7 days.
        iii. Staining of Carious Lesions: SDF permanently stains carious lesions dark brown or black, which may have cosmetic implications. However, this staining indicates that the lesion has been arrested.
        iv. Temporary Skin Staining: If spilled on the skin, SDF can cause a temporary brown discoloration, lasting up to two weeks. Immediate washing with soap and water reduces the staining.

    b. Long-Range Risks:
        i. Cosmetic Impact of Staining: The permanent dark staining of arrested carious lesions may have psychosocial effects in participants who are concerned about aesthetics.
            1. Mitigation: The application of silver diamine fluoride is limited to carious lesions on the back teeth, in keeping with previous study findings that indicate staining on posterior teeth is more acceptable than staining on anterior teeth, and oral-health related quality of life in children receiving silver diamine fluoride is non-inferior to those receiving sealants and ART at least 6 months post-treatment.

    c. Rationale for the Necessity of Exposing Participants to These Risks:
        i. The study aims to provide non-invasive, cost-effective, and Medicaid-reimbursable dental care for underserved populations. The benefits of preventing and arresting tooth decay outweigh the minimal risks involved.

    d. Why the Value of the Information Gained Outweighs the Risks:
        i. The study will generate real-world evidence on the effectiveness of SDF in school-based settings, which is critical for improving oral health programs, especially for underserved populations.

    e. Alternative Procedures Considered:
        i. Traditional restorative, surgical dental treatment (e.g., fillings, crowns) was not selected due to its invasiveness, high cost, risk of pain, infection, and need for anesthesia.

2. **Fluoride Varnish (PreviDent and FluoroDose)**
    a. Immediate Risks:

i. Nut Allergy Consideration: Some fluoride varnish formulations contain pine nut derivatives.
    1. Mitigation: FluoroDose (nut-free formulation) will be used for individuals with nut allergies, and PreviDent will be used for individuals without nut allergies.
ii. Mild Irritation: In rare cases, fluoride varnish may cause transient gum or mucosal irritation, which typically resolves within 24 hours.

b. Long-Range Risks: n/a

c. Rationale for the Necessity of Exposing Participants to These Risks:
    i. Fluoride varnish is a widely recommended preventive dental treatment that can significantly reduce the incidence of dental caries, particularly in underserved populations who may lack access to regular dental care.

d. Why the Value of the Information Gained Outweighs the Risks:
    i. Fluoride varnish is known to provide significant caries prevention. This study will provide important data on its effectiveness in a school-based setting, informing future oral health programs for children in underserved communities.

e. Alternative Procedures Considered:
    i. See 1e above.

3. Resin-Modified Glass Ionomer (GC America Fuji IX GP Extra)

a. Immediate Risks:
    i. Post-Application Sensitivity: Some participants may experience transient tooth sensitivity, usually resolving within a few days.

b. Long-Range Risks: n/a

c. Rationale for the Necessity of Exposing Participants to These Risks:
    i. Resin-modified glass ionomer is a widely used material for dental restoration that is cost-effective, provides fluoride release to help prevent further decay, is hydrophilic (which is useful in non-traditional dental care environments where requisite isolation of the dental tissues from saliva may prove difficult), and is well-suited to the non-invasive treatment of dental caries.

d. Why the Value of the Information Gained Outweighs the Risks:
    i. The data from this study will help determine the efficacy and safety of resin-modified glass ionomer in a school-based preventive dental care program, benefiting populations with high dental needs.

e. Alternative Procedures Considered:
    i. See 1e above.

4. Data Storage and Privacy Risks

a. The study will involve the storage of both participant data and associated clinical information, which will be managed with the highest regard for security and confidentiality.
    i. Database Security: All participant data will be stored securely on secure New England Survey System (NESS) Servers.
        1. Access to this database will be controlled by password protection, and only coded information will be entered to ensure privacy.
        2. Electronic communication with outside collaborators will strictly involve anonymized data. The database features an electronic audit trail that logs any changes to data, including the user and timestamp of changes.
    ii. Source Documents: Source documents include informed consent forms, health histories, clinical care records, and examination details. These are collected via Apple iPads and

stored on a secure server at NESS. Both iPads and the programming utilized to access study records are password-protected to ensure data integrity and secure access. No school records will be collected. No information regarding participating children's school performance will be collected. Only information needed to perform clinical interventions will be collected. As a result, FERPA does not apply and IRB approval from the Department of Education is not needed.

b. Risks Associated with Data Management
    i. Accuracy and Completeness of Data: Study staff, under the supervision of investigators, are responsible for the collection and documentation of all source data. Ensuring that the data is accurate, complete, and legible is essential for the integrity of the study. Any inconsistencies or unanticipated problems must be addressed promptly by the study team.
    ii. Data Entry and Audit: All data entered electronically via Apple iPads will be reviewed for accuracy. Unusual or out-of-range entries are flagged during semi-annual audits for correction. Additionally, any changes to the data will be tracked by the system's audit trail to ensure that all modifications are justified and transparent.
    iii. De-identification, data access, and security
        1. De-identification and Masking: Identifiable participant information will not be shared with the study investigators. All data will be de-identified prior to being sent to investigators for analysis. The identification code key will not be accessible to study PIs or biostatisticians. Schools and participants will be assigned unique IDs prior to data collection to further minimize the risk of identifiable data being exposed. The following process describes the unique code creation, access, and use:
            a. A child participants in the school-based caries prevention program. Specific to the program, they will have their own electronic health record.
            b. In this health record, a unique identifier is created for each child.
            c. The school-based program uses this identifier to verify their own data entry. Program personnel have access to the full child records.
            d. The program will provide researchers with the identifiers of all children who also consented into the BASICS study
            e. Researchers will randomize the treatment pathway as described in the protocol for all children in #4
            f. Upon completion of the study, data will be sent to researchers. Only the unique identifier will be sent with the other health data, and no other identifying information will be accessible by researchers.

            Only program personnel providing care will have access to identifying information, as part of their standard operating procedure and separate consent process. The code available to researchers is not expected to be needed to identify specific patients for safety purposes or any other reason. Any queries about data for participants can be sent using the unique identifier and verified by the program personnel. At the completion of the study, the unique participant code will be deleted.
        2. Electronic Data Transfers: When data is shared electronically, it will be transmitted over a secure, encrypted private network. In instances of external collaborations, only de-identified data will be communicated.
    iv. Retention of Data
        1. Records Retention: All data records will be stored electronically for the duration of the study on secure NESS servers. These records will be maintained for the term of the study and will be deleted or archived in accordance with NYU Langone Health IRB policies upon completion.
    v. Risks Related to Informed Consent
        1. Informed Consent Process: The informed consent process is conducted via paper.

a. Signed and dated paper informed consent documents will be stored electronically after being collected, with images of the forms captured and stored securely on the iPad in the subject's electronic dental record.

vi. Data Storage and Privacy Risks Mitigation
1. Data Deletion and Access Control: In the event of a staff member leaving the study, their access to data is immediately revoked. Any personal data is securely deleted to protect participant privacy.
2. Regular Audits: Data security will be regularly monitored and audits will be performed to ensure compliance with the security measures outlined above.

2.4.2 Known Potential Benefits

1. Advantage Arrest® Silver Diamine Fluoride (SDF) – Elevate Oral Care
   a. Immediate Benefits:
      i. Appropriate for patients with high-risk sites and all cavity-active patients for primary prevention, incipient, interproximal, and class V decay, decay close to the pulp, and Silver Modified Atraumatic Restorative Treatment (SMART) for enhanced esthetics.
      ii. Caries Arrest: A single application can arrest carious lesions up to 90%.
      iii. Dentin Sensitivity Relief: Provides immediate relief from dentinal hypersensitivity.
      iv. Non-Invasive Application: No need for anesthesia or drilling, making it ideal for patients with limited access to dental care, or with special needs, or those who are medically compromised.
      v. Ease of Use: Comes with a convenient applicator for precise application.

   b. Long-Term Benefits:
      i. Prevention of Caries Progression: Regular applications can prevent the progression of early carious lesions.
         1. All participants will receive either primary or primary and secondary caries prevention twice yearly, with significant reductions in disease prevalence, helping to elucidate the most effective sequence of treatments to reduce participant nonresponse.
         2. The methods to be applied and the outcomes identified both address national Healthy People 2020 goals.
      ii. Cost-Effective: Reduces the need for more expensive restorative procedures.
      iii. Improved Patient Compliance: Non-invasive nature increases patient acceptance and compliance.

2. FluoroDose® Fluoride Varnish – Centrix
   a. Immediate Benefits:
      i. Quick Application: Dries in seconds upon contact with saliva, ensuring minimal chair time.
      ii. Clear Finish: Dries clear, eliminating concerns about tooth discoloration.
      iii. Patient Comfort: Smooth texture without clumping enhances patient comfort during application.
      iv. Flavor Variety: Available in multiple flavors, improving patient acceptance.

   b. Long-Term Benefits:
      i. Caries Prevention: Regular application can reduce caries incidence by 30-35%.
      ii. Enhanced Remineralization: Supports the remineralization of early carious lesions.
      iii. Dentin Sensitivity Management: Provides relief from dentinal hypersensitivity.
      iv. Cost-Effective Preventive Measure: Offers a budget-friendly solution for caries prevention.

3. GC Fuji IX GP Extra – GC America
   a. Immediate Benefits:

i. Fast Setting Time: Allows for final finishing in only 2.5 minutes from initial mix, saving valuable chair time.
ii. Fluoride Release: Offers six times the initial fluoride protection compared to previous versions of this resin modified glass ionomer, aiding in caries prevention.
iii. Aesthetic Appearance: Higher translucency compared to other resin modified glass ionomers, improving the aesthetic outcome of restorations.

b. Long-Term Benefits:
i. All participants will receive either primary or primary and secondary caries prevention twice yearly, with significant reductions in disease prevalence, helping to elucidate the most effective sequence of treatments to reduce participant nonresponse.
1. The methods to be applied and the outcomes identified both address national Healthy People 2020 goals.
ii. Durability: Exhibits robust physical properties, maximizing durability for optimum performance.
iii. Reduced Marginal Leakage: Maintains an excellent marginal seal over time, reducing the risk of secondary caries.
iv. Versatility: Suitable for a wide range of restorative procedures, including use in challenging oral environments.

Ultimately, evidence-based changes in knowledge, attitudes, and practice among all patient and stakeholder partners will help reduce the continually high burden of caries in children, particularly among minority and low-SES children. Improved outcomes data should increase support for the sustainability of ongoing and new caries prevention programs at both a local and national level. The benefits to society include improved oral health for our children, which is sustained by a system of preventive care that is more clinically and cost-effective than the current method of care.

Numerous efficacy trials demonstrate the benefits of preventive dental care using glass ionomer and resin modified glass ionomers for primary and secondary prevention, which has far-reaching effects on physical and emotional health, nutrition, social interactions, and employability. However, numerous barriers still exist to improvements in child oral health: an already-existing global and national burden of caries; the social burden of disease, particularly affecting academic performance and psycho-social development; barriers to office-based care[49]; economic incentives to support treatment rather than prevention; the reduced efficacy of treatment to prevention; and large variation in care without outcome measures of effectiveness.

Without data to support the effectiveness of preventive oral health care, we predict that two things will occur (depending on state and local values and circumstances): 1) the current implementation of well-meaning but ineffective, inefficient, or resource-restricted programs will continue; and/or 2) there will be an extinction of those public caries prevention programs that are truly effective.

From a national perspective, our preliminary data suggest that a school-based caries prevention program that includes silver diamine fluoride, fluoride varnish, and resin modified glass ionomer cements may exceed the goals of *Healthy People 2020*. This information would: 1) set the stage for broader dissemination; and 2) stimulate implementation tests of other “place-based” caries prevention programs for other populations (e.g., mothers, elderly, etc.), in locations where people learn, work, play, and pray.

Long term, we believe that children (and adults) with improved oral health will be better prepared to learn, thrive and improve their social and economic opportunities. These important accomplishments would be one step in reducing social inequalities.

3 Objectives and Purpose

3.1 Primary Objective

1. What is the most effective first-stage treatment for caries prevention, assessed via caries incidence?

3.2 Secondary Objectives

2. What is the most effective sequence of treatments to reduce treatment nonresponse, assessed via caries incidence?
3. What is the optimal dynamic treatment regime given patient attributes, assessed via varies incidence modified by disease severity, sociodemographics, and treatment history?
4. Given alternative strategies, what is the most cost-efficient allocation of resources that can most significantly affect population health, measured by time and cost of care?

4 Study Design and Endpoints

4.1 Description of Study Design

BASICS is a phase-III, single-center, Sequential, Multiple Assignment, Randomized Trial (SMART). It will employ alternative treatment pathways based on initial randomization and subsequent response status, with each pair of pathways defining an adaptive intervention. Four dynamic treatment regimes will be embedded in the SMART (see Study Design Schematic). Study agents and interventions used in BASICS include silver diamine fluoride, glass ionomer dental sealants, silver modified atraumatic restorations, fluoride varnish, and an oral hygiene intervention.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Primary study endpoints include the number of new dental caries observed and the person-level prevalence of dental caries, which reflects the number of participants that did not respond to care (nonresponse). These outcomes were selected as they are standard outcomes for school-based caries prevention programs and they directly link to measuring treatment nonresponse.

4.2.2 Secondary Study Endpoints

The secondary study endpoints are costs and cost differences between sequential treatments (arithmetic means). These endpoints were selected as there is significant variation in school caries prevention program design and implementation that is unaccounted for in economic evaluations, highlighting the lack of robustness in economic studies of dental interventions.

4.2.3 Exploratory Endpoints

Not applicable.

5 Study Enrollment and Withdrawal

To facilitate recruitment, enrollment, treatment, and data collection, BASICS will be implemented in an existing school-based caries prevention program that already provides the same treatments proposed in the study. The SBCP program will collect informed consent (for program participation) and school MOUs as part of its natural program operation. Any child participating in the SBCP program will be eligible to participate in the BASICS study. All parents and guardians of program participants will be sent a BASICS study information sheet and separate informed consent document for participation in the study. A minimum of ten schools from the SBCP program will be included in the BASICS study.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Be enrolled in participating schools
2. Be between the ages of 5 and 13 years
3. Provide parental/guardian informed consent
4. Child assent

5.2 Exclusion Criteria

Participants with any of the following criteria will be excluded from participation in this study:

1. ulcerative gingivitis or stomatitis
2. known sensitivity to silver or other heavy-metal ions
3. more than six affected sites
4. those who have had full mouth gingivectomies
5. patients showing abnormal skin sensitization in daily circumstances
6. those who have had pulp capping
7. patients with a known sensitivity to ingredients including colophony (kolophonium) and rosin
8. known allergic reaction to fluoride

These criteria will be confirmed by the study dentist prior to performing the study procedures and by parental attestation in the consent form.

5.3 Vulnerable Subjects

This study primarily involves children.

5.4 Strategies for Recruitment and Retention

All children in eligible grades in participating schools will receive informational sheets along with study consent documents. Study documents (parent information sheet and permission form, child assent) will be given to the participating SBCP, which will then include study documents with the other consent forms used by the SBCP. The SBCP will direct children to take sheets home and give them to the parent or guardian. The recruitment plan does not use any NYULH media services. All recruitment materials (informational sheets) will be submitted for approval by the IRB. Women and minorities will be included (approximately 50% women and 15% minority).

After signature by parents/guardians, the signed consent form will be returned to the school and collected by study investigators. The treating dentist will then sign the parental permission form once it is returned by parents.

Assent from children will be obtained by the treating dentist prior to the study treatment.

5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will not utilize DataCore/EPIC for recruiting purposes.

5.5 Duration of Study Participation

Participants are expected to participate for a minimum of 2.5 years

5.6 Total Number of Participants and Sites

Recruitment will end when approximately 1200 participants are enrolled. It is expected that approximately 3000 participants will be invited to participate in order to produce 1200 evaluable participants.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate 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 participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Handling of Participant Withdrawals or Termination

As a pragmatic trial, it is accepted that enrolled children – who are students at participating schools – may be lost to follow-up (e.g., moved away, enrolled in another school, or other reason). As a result, no attempts will be made to follow-up with withdrawn or terminated participants.

5.8 Premature Termination or Suspension of Study

This study may be temporarily 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 Principal Investigator Ryan Richard Ruff and the National Institutes of Minority Health and Health Disparities (funder). If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent and/or Procedural Intervention

6.1.1 Acquisition

All study agents will be purchased directly from their respective manufacturers or approved dental suppliers:

1. Advantage Arrest is manufactured and distributed by Elevate Oral Care.
2. Fluoride Varnish is acquired from standard dental supply vendors.
3. GC Fuji IX is produced by GC America and is purchased through commercial dental distributors.

Study products will be stored and handled by the principal investigator and study staff at the clinical site.

6.1.2 Formulation, Appearance, Packaging, and Labeling

All products are commercially marketed and labeled appropriately for human dental use. No relabeling or repackaging will be conducted.

1. Advantage Arrest™: 38% Silver Diamine Fluoride. Dark blue liquid in 8 mL dropper bottles. Supplied in labeled, sealed containers from Elevate Oral Care.
2. Fluoride Varnish: 5% Sodium Fluoride. Dispensed in single-use packets or “lollipacks.” Viscous pale yellow gel.
3. GC Fuji IX: pre-capsulated glass ionomer restorative material. Self-curing. Provided in labeled blister packaging.

6.1.3 Product Storage and Stability

All agents will be stored according to manufacturer recommendations:

1. Advantage Arrest: Store at room temperature, protected from light. Stable until expiration if unopened. Shelf life ~2 years. Stored in a combination-locked mobile chest.
2. Fluoride Varnish: Store at room temperature. Single-use packets or “lollipacks” are stable until expiration. Stored in a combination-locked mobile chest.
3. GC Fuji IX: Store in a cool, dry area. Once a capsule is activated, it must be used immediately.

All opened multi-dose products (if applicable) will be discarded per manufacturer's guidelines and local infection control policy.

6.1.4 Preparation

All preparation will be done by licensed dental professionals or trained study staff under clinical supervision.

1. Advantage Arrest: No reconstitution. Applied directly using microbrush applicators.
2. Fluoride Varnish: Dispensed from single-use packets or “lollipacks”. No preparation needed.
3. GC Fuji IX: Mixed using an amalgamator per manufacturer's instructions.

6.1.5 Dosing and Administration

Doses are not weight-based. All products are administered by licensed dental professionals or trained study staff under clinical supervision during the clinical visit which takes place during traditional school hours. There are no self-administered components.

1. Advantage Arrest: 1-2 drops are dispensed to a dappen dish or mixing well and applied per site with a microbrush, once per lesion or sound tooth. Application time: ~30 seconds scrubbing with a minimum 1-minute drying time.
2. Fluoride Varnish: Applied to all tooth surfaces post-cleaning. 0.3-.4mL per child. Applied with brush, allowed to set with saliva.
3. GC Fuji IX: Mixed and placed into cavities using appropriate applicators and finger-sweep technique. Sets chemically in under 6 minutes.

6.1.6 Route of Administration

All products are administered **topically to teeth** in the oral cavity.

6.1.7 Starting Dose and Dose Escalation Schedule

All products will be used at standard clinical dosages as indicated for routine application. No dose escalation will occur.

6.1.8 Dose Adjustments/Modifications/Delays

Dose modifications are not anticipated. If a participant develops hypersensitivity, ulceration, or other adverse effects, the product will be discontinued. Adverse reactions are expected to be rare but will be monitored.

6.1.9 Duration of Therapy

Participants will be followed for up to five visits post-treatment for outcome evaluation and re-/treatment.

1. Advantage Arrest: Single-visit placement or bi-annual application in line with protocol
2. Fluoride Varnish: Bi-annual application
3. GC Fuji IX: Single-visit placement or bi-annual evaluation for retention and replacement as needed, in line with protocol.

6.1.10 Tracking of Dose

Applications will be documented in a secure (NESS) dental chart. Each agent's use per visit will be recorded with tooth number, location of lesion (as applicable), and operator name and signature. Regular reconciliation will confirm accuracy.

6.1.11 Device Specific Considerations

Not applicable – No devices are being tested in this study.

6.2 Study Agent Accountability Procedures

All study products will be tracked using a supply inventory tracker maintained by study staff. This log will include:

1. Expiration date
2. Quantity received
3. Remaining inventory

Unused or expired product will be discarded per manufacturer and site policy. No products will be returned to the manufacturer. Reconciliation will be conducted monthly and at study closeout.

6.3 Study Procedural Intervention(s) Description

The procedural interventions in this study include non-invasive caries arrest and restoration treatments:

1. Topical application of silver diamine fluoride
2. Application of fluoride varnish
3. Placement of atraumatic restorations (ART) using GC Fuji IX

Each is delivered during routine clinical visits by licensed dental providers in accordance with the manufacturer's instructions.

6.3.1 Administration of Procedural Intervention

All interventions will be administered by licensed dentists or dental hygienists. Any individuals administering the intervention (those individuals providing care as part of the SCHOOL-BASED DENTAL PROGRAM) will be first added to the study and approved as investigators prior to their involvement.

Each visit will last approximately 7-12 minutes, on average. Fluoride varnish may be reapplied at 6-month intervals. Silver diamine fluoride and sealants or ART with Fuji IX will be placed during the initial and subsequent 6-month intervals, with bi-annual evaluation for retention and replacement as needed, in line with protocol. At least 5 visits are proposed for participants in this study.

6.3.2 Procedures for Training of Clinicians on Procedural Intervention

All participating clinicians will be trained and standardized before enrolling participants. A standard operating procedure (SOP) will be developed and distributed. Periodic training and standardization sessions will occur every 12 months to ensure procedural consistency. Training and standardization exercises will involve the use of case reports and relevant intraoral images, typodonts, and live patients not included in the study.

6.3.3 Assessment of Clinician and/or Participant Compliance with Study Procedural Intervention

There is no assessment of participant compliance, as all treatments are provided by the school-based caries prevention program. Clinician compliance will be assessed by comparing the de-identified electronic health record data with the corresponding pathway from the research design. Any evidence of mis-match between what patients should have received and actually received will be recorded, noted in study notebooks, and communicated to the school-based caries prevention program.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

All treatments listed in the schematic for the BASICS experimental study are already provided by participation in the school-based caries prevention program. Thus, procedures described in section 7.1.1 are already established

in the program. In this proposed study, we will be changing the order of treatments based on the longitudinal oral health needs of participants. Thus, the research component of this study is to explore the impact of the variation in treatment scheduling and sequence on oral health.

All of the included procedures can be expected to be provided outside of the study, but the study specific procedures will modify the order of the procedures that are provided.

7.1.1 Study Specific Procedures

While the following procedure are provided as part of the operations of the SBCP, they are included as study-specific as well as these are the accepted procedures for the treatments selected for the study.

At each study visit, a clinician will perform full-mouth visual-tactile oral examinations using a disposable mirror, disposable explorer, and head lamp with participants laying in a portable dental chair. Teeth will be assessed as being present or missing intraorally. Individual tooth surfaces will be assessed as being intact/sound, sealed, restored, decayed, or arrested. Caries diagnosis will use the International Caries Detection and Assessment System (ICDAS) scoring criteria for 5 (distinct cavity with visible dentine) or 6 (extensive distinct cavity with visible dentine) [27, 28].

At the baseline observation, the enrolled population will be randomized to receive a first-stage treatment of either silver diamine fluoride (Trajectory 1) or dental sealants with atraumatic restorations, where indicated (Trajectory 2). Children in the initial SDF group will receive the treatment on sound posterior dentition and any posterior teeth with untreated decay. Children in the sealant and ART group will receive either treatment on posterior dentition based on the presence of untreated caries. In both groups, treatment will be applied in the absence of pain, abscess, or infection

Nonresponse will be determined at the second and third post-baseline observational periods by the diagnosis of any dental caries on posterior dentition, including any new caries on previously sound dentition (primary prevention failure) or any teeth diagnosed at baseline with caries that failed to demonstrate arrest (secondary prevention failure). The total number of caries will also be recorded. Responders to either first stage treatment will continue to receive biannual screenings for retention and responsiveness. Non-responders will subsequently proceed to second-stage randomization.

Nonresponders in Trajectory 1 will receive a second-stage randomization to either SDF reapplication plus fluoride varnish receipt of an electronic toothbrush, or an SDF reapplication plus dental sealants. As nonresponse is determined by the diagnosis of new caries, this latter pathway will take the form of delayed silver-modified atraumatic restorative treatment (delayed SMART) [22, 23] on any affected teeth and application of sealants to any remaining sound dentition. Similarly, nonresponders in Trajectory 2 will be randomized to either an augmented treatment of sealant reapplication (including atraumatic restorations) plus fluoride varnish and receipt of an electronic toothbrush or an intensified protocol of SMART on affected dentition. Caries incidence will continue to be evaluated at each remaining planned observation.

Additional design procedures include (1) any patients with sealants that are not retained but no decay is indicated will be considered responsive and the sealant will be reapplied; (2) any patients with atraumatic restorations that are not retained will be considered non-responsive, as it cannot be robustly determined if there is no new decay; (3) any responding participant who transitions to nonresponse after the predetermined nonresponse periods will continue to receive their original first-stage intervention and the total days that elapsed before nonresponse was observed will be recorded; (4) any nonresponding patient who continues to fail to respond will receive reapplication/reinforcement of their second-stage intervention; (5) any new dentition that erupts in either Phase 1 or Phase 2 will receive the corresponding treatment for that phase (e.g., first-stage or second-stage randomized treatment).

7.1.2 Standard of Care Study Procedures

The oral examination and treatment with silver diamine fluoride, fluoride varnish, and dental sealants are considered part of regular standard of clinical care. All of the included procedures can be expected to be provided outside of the study, but the study specific procedures will modify the order of the procedures that are provided.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Not applicable.

7.2.2 Other Assays or Procedures

Not applicable.

7.2.3 Specimen Preparation, Handling, and Storage

Not applicable.

7.2.4 Specimen Shipment

Not applicable.

7.3 Study Schedule

All of the visits described below are part of the research study. Study participants are still part of the school-based caries prevention program at the same time.

7.3.1 Screening

Screening (Day -28 to -1)

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review dental history to determine eligibility based on inclusion/exclusion criteria.
- Schedule study visits for participants who are eligible and available for the duration of the study.

7.3.2 Enrollment/Baseline

Enrollment/Baseline Visit (Visit 1, Day 0)

- Obtain informed consent of potential participant, if not obtained in Screening period
- Verify inclusion/exclusion criteria.
- Perform comprehensive oral examination
- Administer the study treatment following first-stage randomization (See Figure 1):
    - Either silver diamine fluoride or glass ionomer cement sealants

7.3.3 Intermediate Visits

7.3.3.1 Visit 2

(Day 160-200)

- Record adverse events as reported by participant or observed by investigator.
- Perform comprehensive oral examination
- Record patients responsiveness status
- Proceed with second stage randomization if determined by comprehensive examination to be in treatment nonresponse (See Figure 1)
- Administer relevant treatment as indicated by second stage randomization

7.3.3.2 Visit 3

(Day 340-380)

- Record adverse events as reported by participant or observed by investigator.
- Perform comprehensive oral examination

- Record patients responsiveness status
- Proceed with second stage randomization if determined by comprehensive examination to be in treatment nonresponse (See Figure 1)
- Administer relevant treatment as indicated by second stage randomization

7.3.3.3 Visit 4

(Day 520-560)

- Record adverse events as reported by participant or observed by investigator.
- Perform comprehensive oral examination
- Document clinical outcomes
- Maintain treatment as indicated in Subgroup (Figure 1)

7.3.3.4 Visit 5

(Day 700-740)

- Record adverse events as reported by participant or observed by investigator.
- Perform comprehensive oral examination
- Record patients responsiveness status
- Document clinical outcomes
- Maintain treatment as indicated in Subgroup (Figure 1)

7.3.4 Final Study Visit

Final Study Visit (Visit 6, Day 880-920)

- Record adverse events as reported by participant or observed by investigator.
- Perform comprehensive oral examination
- Record patients responsiveness status
- Document clinical outcomes
- Provide all participants with any needed care (dental sealants on sound dentition, ART or SMART on any carious posterior dentition, in accordance with Figure 1)

7.3.5 Withdrawal/Early Termination Visit

If the patient is willing, a final comprehensive exam will be provided if a subject withdraws from the study.

7.3.6 Unscheduled Visit

There are no unscheduled visits.

7.4 Concomitant Medications, Treatments, and Procedures

Concomitant medications are not applicable. However, concomitant treatments and procedures that are observed through oral examinations (e.g., care provided by an external dentist, such as evidence of teeth with fillings that were not observed previously) will be noted in EHRs.

7.5 Justification for Sensitive Procedures

Not applicable.

7.5.1 Precautionary Medications, Treatments, and Procedures

Not applicable.

7.6 Prohibited Medications, Treatments, and Procedures

Not applicable.

7.7 Prophylactic Medications, Treatments, and Procedures

Dental sealants, silver diamine fluoride, and fluoride varnish are preventive care.

7.8 Rescue Medications, Treatments, and Procedures

Should children experience caries are treatment with SDF or dental sealants, we will provide SDF (for caries management), atraumatic restorations, or silver modified atraumatic restorative treatment.

7.9 Participant Access to Study Agent at Study Closure

Not applicable.

8 Assessment of Safety

8.1 Specification of Safety Parameters

All interventions provided in this study are standard of care; there are no safety parameters that are study endpoints. Any adverse events experienced will be recorded in patient electronic health records and reported according to the guidelines described in Section 8.

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. 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)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. AE's will be classified on the following criteria:

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 Expectedness

PI Ruff and Medical Monitor Barry Godín will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

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

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

Adverse events will be reported regardless of the relationship to the study interventions to the IRB within the required timeframe for adverse event reporting as specified in the IRB Reportable Events Guidelines for required timeframe for reporting to the IRB.

8.4.2 Serious Adverse Event Reporting

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the IRB and PCORI in accordance with requirements:

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the Medical Monitor within 3 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 7 days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the IRB in accordance with their requirements and will be reported to NIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NIH on an annual basis by way of inclusion in the annual report and in the annual AE/DSMP summary which will be provided to NIH.

We note that no clinical adverse events are expected.

8.4.3 Unanticipated Problem Reporting

Any incidents or events that meet the OHRP criteria for UPs will result in the creation and completion of an UP report form. The site investigator will report Ups to the IRB and to the NIMHD. Each UP report will include:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

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

- UPs that are SAEs will be reported to the IRB and to the NIMHD within 7 day of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the NIMHD within 15 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 7 days of the IR's receipt of the report of the problem from the investigator.

8.4.4 Reporting of Pregnancy

Not applicable.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the NIMHD within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the NIMHD within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the NIMHD and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Reporting Procedures – Notifying the FDA

Any study event associated with the included medical devices in this study will be reported to the FDA. All events must be associated with the use of the device and unexpected. Any event that is fatal or life-threatening will be reported in 7 calendar days, and any that are serious but not fatal or live threatening, or a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting, will be reported within 15 calendar days.

8.7 Study Halting Rules

Given the 30-year history of the study investigators, we know of no safety issues that would prompt suspension of enrollment or the interventions. However, if we encounter serious, unexpected, and related AEs, the PIs, PCORI, and the IRB would confer to determine whether findings might trigger a safety review based on the number of overall SAEs, the occurrence frequency of the type of SAE, severe AEs/reactions, or increased frequency of events. There are no stopping rules needed for this study.

8.8 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at each site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. An independent medical monitor will be appointed. The PI and sub-investigator Godín are responsible for data safety monitoring reviews. This includes conducting systematic and periodic reviews of aggregate data and adverse events. These specific data and events include staining due to silver diamine fluoride or allergic reaction to fluoride varnish. These data and events will be reviewed quarterly. These reviews will be disseminated to sites via email.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- The clinical monitor, who is a licensed, board-certified pediatric dentist with experience implementing clinical research studies for school-based oral health programming, will conduct the monitoring on-site during annual trainings and assessments typically taking place during either the first two weeks of the academic school year, or the first two weeks of the Spring semester. Training will be comprehensive in nature to reflect fidelity to study intervention protocols, including data acquisition, clinical compliance, infection control, and data security, and be complimented by the authoring of quality assessment and improvement reports for review by the PI.
- Chairside audits will be conducted by the clinical monitor to ensure monitoring practices are performed consistently by all participating study personnel.
- Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

A formal SAP will be completed prior to database lock and logged with the IRB.

10.2 Statistical Hypotheses

The null hypothesis is that there is no difference in treatment nonresponse between first stage assignments (SDF compared to dental sealants). The alternative hypothesis is that they are different. The study is a superiority trial. Endpoints will be evaluated at the end of the treatment nonresponse observational window (Study visit 3) and at the completion of subsequent visits (Study visit 4, 5, and 6).

10.3 Analysis Datasets

Analytic datasets will include intention-to-treat (all randomized participants) and per-protocol (those who completed enough visits sufficiently to ensure the full time for nonresponse has been observed, through third visit)

10.4 Description of Statistical Methods

10.4.1 General Approach

BASICS is a phase-III Sequential, Multiple Assignment, Randomized Trial (SMART) (described fully in the Schematic of Study Design). Descriptive statistics will use percentages and counts for persons with dichotomous outcomes and means/standard deviations for continuous outcomes. For inferential tests, the p-value used for statistical significance (Type 1 error) is 0.05, and all tests are two-tailed.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary efficacy endpoints include the best initial treatment for dental caries and the best treatment sequence for nonresponders. This is equivalent to the main effect of the first-stage treatment and additional clinically-relevant contrasts (see Statistical Analysis Plan for further description). Data will be analyzed according to intent to treat. The main effects will be assessed using generalized linear mixed logistic regression (for presence/absence of dental caries and presence/absence of treatment nonresponse) and negative binomial regression (for caries incidence). Predictors include semester of entry, the interaction between semester and treatment trajectory, and any relevant demographic variables. Any instance of missing data will be accounted for using time-ordered nested conditional imputation.

10.4.3 Analysis of the Secondary Endpoint(s)

Secondary endpoints in BASICS include the best dynamic treatment regime, the optimal adaptive intervention, and costs of adaptive interventions. Analysis for the best adaptive intervention will utilize weighting and replication and other methods (see Statistical Analysis Plan). Analyses for identifying the optimal adaptive intervention will use Q-Learning (see SAP).

For cost analyses, we will quantify the economic costs of dynamic treatment regimes in school-based caries prevention will using microcosting in tandem with time studies. We will take a bottom-up microcosting approach to data collection. The bottom-up approach to microcosting is characterized by quantifying resource utilization for each cost item, and then aggregating to the individual or system-level, as opposed to assessing system costs and then allocating to individual cost items (top-down approach).[73] This approach is more accurate for labor-intensive services than microcosting with a top-down approach. [74-76] We will use the following tools to capture costs:

1) Standardized comprehensive templates to collect resource unit quantity and unit cost data, especially fixed costs (i.e. patient chairs, operating stools, dental lights, and other equipment), wage rates, fringe benefits, and material costs. These data templates will be filled out using retrospective administrative data (i.e. financial records, time sheets, program documents).
2) Time stamp data generated through the on-site clinical outcomes database, which serves to quantify the amount of time spent on clinical examinations and treatment per student. This is already built into our iPad electronic health record system.
3) Electronic time study logs that ask clinicians at 15-minute intervals during the workday about their current activities; [77] both clinical activities (i.e. set-up time and delivering the intervention) and research/administrative activities (i.e. staff meetings, billing/verifying insurance coverage, and downtime) can be tracked and costs captured for each type of activity.

We will take two approaches to costing-microcosting with and without the time study data. The microcosting without the time study data will combine data from the first two data collection approaches, while microcosting with the time study data will combine all three data collection approaches. Though the time stamp data captures the treatment time per child, it is unclear to what extent clinicians spend non-treatment time on activities related directly to the clinical interventions vs. research/administrative activities. Microcosting without the time study data then necessitates imposing the assumption that all the billed time by dental hygienists is related to clinical activities, making it likely that intervention costs will be overestimated across all sequential treatments. In contrast, microcosting with the time study data will allow us to precisely identify when clinicians are undertaking activities directly related to the intervention.

We will quantify intervention costs from the perspective of the agency providing dental care to schools through school-based caries prevention programs over the 2.5 years used to provide the sequential interventions. This will determine the funding needed for to set up and operate the program. We assume that the providing agency does not see students for dental care outside of the school-based caries prevention programs. We will capture the cost of dental materials and equipment, office equipment, space needs, and educational/promotional materials using internal accounting data. We will then quantify value of resources used for each patient as (resource cost*quantity used per patient). We will capture the time spent by personnel on training and delivering care through the electronic time study logs. Time costs are estimated by multiplying the time spent on activities by the U.S. Bureau of Labor Statistics for each type of personnel. The cost of healthcare resources for each treatment pathway will be estimated both at the individual patient level and by the type of sequential treatment. Because we are valuing costs over a 2.5 year timeframe, we will discount costs by 3%. We will follow validated economic evaluation checklists for quality and reproducibility.[78]

We will then use multivariable regression to analyze the difference in economic costs based on responder status, providers, schools, state legislation, and observable student characteristics (i.e. race, gender). To account for missing data, which may come about if participants drop out, we will use multiple imputation to avoid eliminating cases with incomplete data. If the amount of missing or incomplete data is small (i.e. <5% of observations) and patterns of missing data are similar across intervention groups, we will additionally conduct analyses that use only complete data.

10.4.4 Safety Analyses

Adverse events will be summarized using descriptive statistics during treatment. No other safety endpoints are included. AEs will be coded following the Medical Dictionary for Regulatory Activities and counted only once for a given participant. Frequencies and severities will be presented, including when the AE was documented. AEs will be ascertained by the study clinician and reported by the PI to the IRB.

10.4.5 Adherence and Retention Analyses

As all treatments in this study are directly provided by a clinician to the patient, there is no measure of adherence to the protocol. However, we will provide descriptive statistical information of the number of patients lost to follow-up or changed schools within the study. Where possible, we will attempt to ascertain the reasons for discontinuation of the study, however in our experience in pragmatic school-based trials this usually stems from participants leaving the school district.

10.4.6 Baseline Descriptive Statistics

Intervention groups will be compared on standard baseline characteristics and prognostic indicators. Full description is included in the Study SAP.

10.4.7 Planned Interim Analysis

BASICS is a sequential, multiple-assignment, randomized trial. By definition this includes interim analysis for treatment responsiveness, followed by second-stage randomization. Full description is included in the Study SAP.

10.4.7.1 Safety Review

As all treatments are standard of care, there are no safety endpoints beyond adverse event reporting.

10.4.7.2 Efficacy Review

Efficacy endpoints include treatment responsiveness after stage-1 and stage-2 randomization phases. Full description is included in the Study SAP.

10.4.8 Additional Sub-Group Analyses

Planned subgroup analyses by select tailoring variables are included in the study SAP.

10.4.9 Multiple Comparison/Multiplicity

Despite multiple comparisons arising from multiple DTRs in a SMART trial, adjustment is often not performed in the literature. Multiple comparisons are minimized in listed objectives (see SAP), but we will also include methods to account for multiplicity including Benjamini & Hochberg and Multiple. Further description is included in the Study SAP.

10.4.10 Tabulation of Individual Response Data

Individual patient descriptive data will be summarized overall, by subgroup, and by observation.

10.4.11 Exploratory Analyses

SMART trials support specific hypothesis-generating analyses using Q-learning, which is described in the study SAP.

10.5 Sample Size

Sample size calculations for Objective 1 are computed for the main effects of the specified experimental design, including the main effects for first-stage treatment (A+B+C vs D+E+F) and the main effects for second-stage treatment in nonresponders (B+E vs C+F). These main effects are equivalent to a longitudinal comparison of two parallel groups in a randomized trial [45]. We assume a within-person correlation of 0.5, a study drop-out rate of 10% (with the difference offset by newly enrolled children each year), a desired power of 0.85, and an alpha of 0.05. This yields a total sample size of 122 for a medium effect size (Cohen's d=0.5). As a result, our anticipated

sample size is sufficient for even small to medium effects at acceptable power levels. We subsequently propose sampling more subjects to support investigation of effect modifiers or subgroup comparisons (e.g., A+B, A+C, D+E). For second-stage treatment main effects, additional considerations are needed for the rate of nonresponse [45]. We assume nonresponse rates are equal across first-stage treatment assignments, and further assume an average nonresponse rate of 30% (as informed by prior studies). This yields a total N of 122/0.3 = 406, or N=203 for first-stage treatment groups and 101 in each nonresponse group (B+E and C+F).

For Objective 2, we estimate power based on the Multiple Comparisons with the Best (MCB) methodology for comparing our embedded DTRs while accounting for multiple comparisons, thereby increasing power [46]. We assume a type 1 error rate, now viewed as the probability of excluding the best DTR from the set of all DTRs, of 5%. We estimate the expected power given our anticipated final sample size assuming the same 10% yearly dropout rate (N=840) for four DTRs, with a minimum effect size of 0.1: $Power_{\alpha,n}=\left(\Sigma,\Delta,\Delta_{min}\right)\geq 1-\beta$. We assume the most conservative case as possible by setting all other DTRs to be the minimum detectable effect size away, compared to DTR(1) ($\Delta_i=\Delta$ ¿. We also assume that correlations between DTRs are equal, in keeping with recommendations. This yields a power of >99%, and the study is well powered even for exceedingly small effect size differences. Finally, as optimization using Q-learning is considered hypothesis generating in the SMART framework, we do not estimate power for this analysis.

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

BASICS employs a multistage randomization design. In the first stage, participants will be randomized at the individual level to receive either silver diamine fluoride or dental sealants. In the second stage, participants identified as nonresponders will be further randomized at the individual level to each respective adaptive intervention (B, C, E, or F). Randomization will utilize adaptive randomization and be performed by the data collection software provided by New England Survey Systems (NESS).

As this study is a pragmatic trial providing physical interventions, blinding/masking is not possible for the clinical investigators. Additionally, as some interventions create physical changes that are observable (e.g., staining from SDF), patients too cannot be blinded. However, final the final statistical analysis can be masked by recoding of subgroups (See Figure 1).

10.6.2 Evaluation of Success of Blinding

Not applicable.

10.6.3 Breaking the Study Blind/Participant Code

Not applicable.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct

such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

As described, this study will be conducted in an existing school-based caries prevention program known as SCHOOLYARD SMILES. The SBCP program will collect consent from parents/guardians of children in order to receive care in the SBCP program. For participation in this study, we will collect additional consent form the parent using a parent permission form, provided in our IRB application. This parent permission form describes the specific study procedures separate from the operations of the program, the risks, and the benefits. Children will then provide assent after being read an assent form, also included in the IRB application. Because of this arrangement, parents signing the consent and children providing assent will not have prior discussion with the study team, although contact information for the study PI is provided to each parent or guardian.

Participation in the study is open to any child participating in the school-based caries prevention program. We will ensure all consent and parent information documents will be in other languages. Prior to the distribution of any consent and informational materials, we will work with the program to identify other primary languages spoken at home for parents with children in the program and have the documents translated and reviewed for IRB approval.

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol: informed consent, Key Information.

13.3.2 Consent Procedures and Documentation

Participation in the BASICS study will be available to any child participating in the SBCP program. By participating in the SBCP program, children will provided informed consent to receive the care provided in the SBCP program. Additional consent documents and informational materials will be provided to SBCP program participants for participation in the BASICS study. Parents or guardians will be asked to sign the BASICS informed consent to be enrolled in the study. Child assent will be obtained prior to treatment at each study visit. The BASICS informed consent document details the risks and possible benefits of participations, and explains the research study.

Participation in the BASICS study includes exclusion criteria as described in section 5.4: participants will be excluded if they have a known allergy to silver.

The participants may withdraw consent at any time throughout the course of the trial. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

All children in eligible grades in participating schools will receive informational sheets along with any study consent documents. Documents will be provided to schools by study investigators for distribution to enrolled children. The recruitment plan does not use any NYULH media services. All recruitment materials (informational sheets) will be submitted for approval by the IRB. Women and minorities will be included (approximately 50% women and 15% minority).

Consent will be returned to the school and collected by study investigators. Information to be collected on consents includes name, age, and sociodemographic criteria. Additional information collected includes whether the child has any medical conditions or special needs, whether they have a known sensitivity to silver or other heavy metal. Only study investigators will receive this information and used for enrollment reporting and subsequent analysis (where indicated in Section 10).

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record.

13.1 Posting of Clinical Trial Consent Form

Not applicable.

13.2 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of the clinical information relating to participants. Therefore, 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.

The study monitor, other authorized representatives of the sponsor, and representatives of the IRB may inspect all documents and records required to be maintained by the investigator. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Inputted data are locally stored on devices and securely transmitted to cloud storage once a cellular or WiFi connection is accessible. End-to-end encryption is utilized at all stages of storage transfer and each iPad is password protected and uniquely assigned to each clinician. Uploaded data is stored in a secure SQL dbase. Our system includes a real-time reporting engine that provides functionality for CRO and sites to review trial patient data and site/patient/visit operations. This supports standard and ad-hoc reporting and CTMS equivalent reports, as well as annotated CRF and patient CRF documents. The system has a comprehensive date- and time-stamped audit trail of any operation made by any user in the system. Our system was developed in collaboration with New England Survey Systems (NESS), which has provided survey and clinical data management systems used by other groups for Phase I through Phase IV drug, vaccine, and device industry trials/studies. The system is fully validated and compliant to 21 CFR Part 11, HIPAA, GDPR, and other standards. Study configuration files (XML) and data files are available automatically and transmitted to study investigators on a set schedule for data cleaning and analysis. Data export capabilities of the system supports over 30 formats including SAS transport datasets and CSV files. Upon receipt, all data will be stored on TrialMaster.

13.2.1 Research Use of Stored Human Samples, Specimens, or Data

Not applicable; no human samples or specimens are collected.

13.3 Secondary Future Use of Stored Biospecimens and/or Data

There are no biospecimens collected in BASICS.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Prior to Study Visit 1, data from completed informed consents will be transmitted into our study Electronic Health Record System. Clinical data throughout the study will then only be entered directly into the EHR:

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered directly into the study EHR, a 21 CFR Part 11-compliant data capture system provided by New England Survey Systems (NESS). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

NESS will transmit data securely to NYU for analysis. Databases are configured to require encrypted connections, data stored in the databases are encrypted at rest (AES-256), and all actions in the database are logged

14.1.1 Data Collection Tools – Mobile Health Technology

Products and Device

The commercial product(s) made by New England Survey Systems [NESS] (mobile apps for tablets will be used to collect study data. The device is commercially available, used as marketed and data is not fed back into the product. The mobile application is also free and commercially available. These devices will be used in accord with the Terms of Service and/or the End User License Agreements (EULA) provided by the product or device vendor. These products and devices will only be used to collect study data with IRB approval and if the subject has agreed to all applicable Terms of Service.

NESS provides survey and clinical data management systems used by other groups for Phase I through Phase IV drug, vaccine, and device industry trials/studies. The system is fully validated and compliant to 21 CFR Part 11, HIPAA, GDPR, and other standards. Study configuration files (XML) and data files are available automatically and transmitted to study investigators on a set schedule for data cleaning and analysis. Data export capabilities of the system supports over 30 formats including SAS transport datasets and CSV files.

Inputted data are locally stored on devices and securely transmitted to cloud storage once a cellular or WiFi connection is accessible. End-to-end encryption is utilized at all stages of storage transfer and each iPad is password protected and uniquely assigned to each clinician. Uploaded data is stored in a secure SQL dbase. Our system includes a real-time reporting engine that provides functionality for CRO and sites to review trial patient data and site/patient/visit operations. This supports standard and ad-hoc reporting and CTMS equivalent reports, as well as annotated CRF and patient CRF documents. The system has a comprehensive date- and time-stamped audit trail of any operation made by any user in the system.

14.2 Study Records Retention

Study documents will be retained for 5 years after closeout of the study.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

The PI and co-investigators will endeavor to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All protocol deviations will subsequently be reported to the NYU Langone IRB.

14.4 Publication and Data Sharing Policy

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

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and

cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post-market surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

This study will be funded by the National Institute on Minority Health and Health Disparities (#R01MD019938).

15.2 Costs to the Participant

There are no costs to the participant.

15.3 Participant Reimbursements or Payments

There are no cash payments. However, some subjects (Subgroups B and E, Study Figure 1) will be provided with an electronic toothbrush with an approximate value of $25 USD.

16 Study Administration

16.1 Study Leadership

The study is led by the Principal Investigator. A committee made up of the PI, the Co-Investigator/Clinical Manager, and the site investigator will meet monthly. We expect to recruit an average of 100 participants per site across 12 study sites (schools), for a total anticipated enrollment of 1200. A site PI (to be determined), who is the investigator overseeing the sites in the SBCP program, will be the primary point of contact supervising activities in each site. The Principal Investigator (PI) will implement a comprehensive management plan to oversee and address unanticipated problems involving risks to participants or others, review interim results, and coordinate protocol modifications across all study sites. The PI will establish regular communication with site investigators through weekly scheduled meetings and written reports to ensure timely identification and reporting of any adverse events or unanticipated problems in accordance with institutional and regulatory requirements. Any unanticipated problems involving risks to participants or others will be reported immediately to the PI and sub-investigator Godín. Interim results as defined in this SMART study are based on the second-stage randomization, as a result, interim analyses are based entirely on treatment nonresponse and defined explicitly in the Statistical Analysis Plan. Any protocol amendments developed by the PI or sub-investigators will be agreed upon by all study investigators and implemented study-wide across all sites.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NIMHD has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.

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Schedule of Events

Activity	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Study team procedures							
Consent	X						
Oral Examination	X	X	X	X	X	X	X
Randomization		X	X	X			
Study device dispensation		X	X	X	X	X	X
Treatment nonresponse determination			X	X			

19 Participating Sites

Site Name	PI Name	Following all procedures outlined within the protocol	Only obtaining informed consent of human subjects	Only obtaining, using, studying, or analyzing private identifiable** information from any source	Only informing prospective subjects about the availability of the research and seeking prospective subjects' permission for investigators to contact them	Other (Please explain)
1. Schoolyard Smiles	Shannon Mills	X				
2.						
3.						
4.						
5.						