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Comparative effectiveness of treatments to prevent dental caries given to rural children in school-based settings: protocol for a cluster randomized controlled trial

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Abstract

Introduction: Dental caries is the most prevalent childhood disease in the world and can lead to infection, pain, and reduced quality of life. Multiple prevention agents are available to arrest and prevent dental caries; however little is known of the comparative effectiveness of combined treatments when applied in pragmatic settings. The aim of the presented study is to compare the benefit of silver diamine fluoride and fluoride varnish versus fluoride varnish and glass ionomer therapeutic sealants in the arrest and prevention of dental caries.

Methods and Analysis: A longitudinal, pragmatic, cluster randomized, single-blind, non-inferiority trial will be conducted in low-income rural children enrolled in public elementary schools in New Hampshire, United States, from 2018-2023. The primary objective is to compare the non-inferiority of alternative agents in the arrest and prevention of dental caries. The secondary objective is to compare cost-effectiveness of both interventions. Caries arrest will be evaluated after two years, and caries prevention will be assessed at the completion of the study. Data analysis will follow intent to treat, and statistical analyses will be conducted using a significance level of 0.05.

Ethics and Dissemination: The standard of care for dental caries is office-based surgery, which presents multiple barriers to care including cost, fear, and geographic isolation. The common intervention used in school-based caries prevention is dental sealants. The simplicity and affordability of silver diamine fluoride may be a viable alternative for the prevention of dental caries in high-risk children. Results can be used to inform policy for best practices in school-based oral health care.

Trial registration: NCT03448107, registered on 2/26/18

Keywords: dental caries; caries arrest; caries prevention; silver diamine fluoride; sealants; interim therapeutic restorations

Strengths and limitations of this study

- Study is a cluster randomized non-inferiority trial
- Study will compare simple and complex interventions for the treatment and prevention of dental caries measured using standard clinical diagnostic criteria
- Statistical and economic analysis will utilize multilevel modeling, generalized additive modeling, and Markov modeling
- Interventions will be randomly assigned at the school level; any child within each participating school that provides informed consent and assent will receive care twice yearly

Background

Dental caries (tooth decay), a gram positive, aerophilic bacterial infection, is the most prevalent childhood disease in the world, estimated to cause a loss of 3.5 million disability adjusted life years [1,2]. If left untreated, dental caries can lead to acute abscess, sepsis, and in rare circumstances, systemic infection and death [3-5]. Untreated dental caries affects more than 20% of elementary school-aged children in the United States, and over 50% of children have ever experienced caries. Among low-income minority children, caries experience can be greater than 70%, and the prevalence of untreated caries exceeds 30% [6-8]. Though the overall prevalence of caries has reduced over the past ten years, sealant use is lowest among low-income children, and less than half of children from low-income families reported visiting a dentist in the previous year [8-10].

The standard of care for dental caries is office-based surgery consisting of local anesthesia, removal of decay using a dental drill, etching of the tooth with acidic gel, application of an amalgam, composite resin, ionomer, gold, or ceramic material, hardening, and polishing [11]. However, office-based care presents multiple access barriers to patients including cost, fear, and geographic isolation [12]. Fewer than 15% of children who accessed an office-based dentist received preventive care [13], many children do not have access to prevention services [14], and those with the least access to prevention have a higher prevalence of oral disease [14]. As a result, many federal and state organizations and institutions recommend the proactive prevention of caries as an alternative to reactive treatment [14-17]. Caries prevention can be provided through traditional office-based care, mobile dental vans, or as part of a school-based dental program, and the comparative effectiveness of these prevention models has been identified as one of the highest-priority research questions by the Institute of Medicine [18].

Common caries prevention agents include water fluoridation, fluoride toothpaste, fluoride varnish, sealants, interim therapeutic restorations or atraumatic restorations, and silver diamine fluoride

(SDF). Individually, each of these preventive treatments has been shown in randomized clinical trials and systematic reviews to be efficacious in the prevention or treatment of dental caries. A review of thirteen trials in children and adolescents found that those treated with fluoride varnish experienced an average reduction of decayed, missing, or filled tooth surfaces of 43% when compared to untreated youth [19]. A systematic review of six trials showed that resin-based sealants significantly reduced the risk of caries in permanent molars up to 48 months compared to no sealants, and estimated that if 70% of control unsealed tooth surfaces were decayed, application of a resin-based sealant would significantly reduce the proportion of carious surfaces to under 19% [20]. Further, there was not sufficient evidence in both systematic reviews and meta-analyses to suggest the superiority of the preventive effects of either resin-based or glass-ionomer sealant material [20,21]. A 2012 meta-analysis of 29 studies indicated that pits and fissures of teeth sealed with interim therapeutic restorations had a mean annual caries incidence over three years of only one percent [22]. Finally, silver diamine fluoride has been shown in reviews to have higher preventive fractions of arrested and prevented caries than fluoride varnish [23], and SDF at 38% concentration applied biannually was more effective in preventing caries than annual applications of lower concentrations [24].

Despite this evidence, the combined effectiveness of different treatments, as well as their feasibility for use in pragmatic settings, is unknown. The objectives of the presented longitudinal, pragmatic, cluster randomized, single-blind, non-inferiority trial are to compare the clinical and cost effectiveness of a simple prevention package (consisting of fluoride varnish and SDF) versus a complex prevention package (consisting of fluoride varnish and therapeutic sealants) in the arrest and prevention of dental caries among low-income rural children in primary school settings. It is hypothesized that simple caries prevention is non-inferior to complex care and is more cost-effective for large-scale implementation.

Methods/Design

This is a longitudinal, pragmatic, cluster randomized, single-blind, non-inferiority clinical trial comparing silver diamine fluoride with fluoride varnish versus therapeutic sealants with fluoride varnish given biannually to children enrolled in public elementary schools in New Hampshire. Prior to the study start, participating schools meeting inclusion criteria will be randomly assigned to receive fluoride varnish/SDF or fluoride varnish/sealants in six-month intervals (±1 month). At each observational period, study participants with informed consent will receive a comprehensive oral examination provided by a licensed dental hygienist (Figure 1) [25,26]. The clinical examination will include an assessment of every tooth and tooth surface for decayed, filled, or missing teeth, as well as pulpal involvement or abscess. Following the oral evaluation, participants will receive the assigned treatments. Any participant presenting with a medical emergency will be referred to school nurses for follow-up care.

This trial protocol is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and has received approval from the New York University School of Medicine Institutional Review Board (#i17-01221). Any changes to the study protocol will be communicated to the IRB and funder in quarterly reports, and investigators will cooperate with any independent audit on behalf of the IRB or funding organization. The study was registered at www.clinicaltrials.gov (#NCT03448107).

Treatment description and regimen

Simple Prevention. One drop (0.05 ml) of silver diamine fluoride (Advantage Arrest ™) solution at 38% concentration (2.24 F-ion mg/dose) will be dispensed per child. Posterior tooth surfaces to be treated will be dried, after which the SDF will be applied with a microbrush to all asymptomatic carious lesions and to all pits and fissures on bicuspids and molar teeth for thirty seconds. Fluoride varnish (5%

NaF) will then be applied to all teeth. Simple prevention will be provided by either dental hygienists or registered nurses.

Complex Prevention. All primary and permanent teeth will be dried prior to application. Pits and fissures on all bicuspids and molar teeth will be sealed with glass ionomer sealants (GC Fuji IX). Glass ionomer sealants (interim therapeutic restorations) will also be placed on all asymptomatic carious lesions. Fluoride varnish (5% NaF) will then be applied to all teeth. Complex prevention will be provided by dental hygienists.

Both arms will also receive toothbrushes, fluoride toothpaste, and oral hygiene instruction. Clinical care will be provided in a dedicated room in each school using mobile equipment and disposable supplies.

Risks and Adverse Events

Each intervention used in this trial is currently employed in clinical practice as a standard of care procedure. The potential risks for study participants are minimal and identical to the risk for children obtaining care in a dental office. The greatest risk is an allergic reaction to fluoride varnish, silver diamine fluoride, or glass ionomer. All adverse events occurring during the study period will be recorded: at each contact with the study participant, investigators will seek information on adverse events by specific questions and an oral examination. Evidence of adverse events will be recorded on electronic health records and appropriate case report forms. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that participation in the study was not the cause. Serious adverse events ongoing at study end will be followed to determine the final outcome. Adverse event reports will be reported to the IRB within five working days from the time investigators become aware of the event.

Definition of outcome measures

Primary outcome measures. Primary outcomes include clinically-evaluated caries arrest and the prevention of new caries. Caries arrest will be evaluated after two years and the prevalence of new caries will be evaluated after five years.

Secondary outcome measures. Secondary outcomes include the comparative cost effectiveness of simple versus complex prevention in the arrest and prevention of dental caries.

Recruitment & Eligibility

In collaboration with the New Hampshire Department of Health and Human Services (DHHS), study investigators identified extant school-based caries prevention programs currently operating in rural counties in New Hampshire. Program officials were contacted to solicit interest in participating in the proposed study. Program officials, in turn, contacted school principals to determine interest in participation. Each participating program and school has confirmed written consent for the study.

Inclusion Criteria. Any existing caries prevention program operating in rural (defined using criteria from the U.S. Department of Agriculture) areas, with official Title 1 status, and located in a health professional shortage area was eligible to participate. All schools within eligible programs were eligible to participate.

Randomization

Participating schools will be block randomized at the school level to receive either the simple or complex treatment using a random number generator. Study statisticians will generate random numbers and assign schools to each number sequence.

Blinding

Due to the nature of the treatments provided, dental hygienists providing care will not be independent from study protocols and therefore are not blinded. Assignment to treatments will follow a predetermined randomization list at the school level, and all students with consent in participating schools will receive the assigned treatment. However, all data analyses for caries arrest will be blinded, as data will be masked prior to analysis such that which schools were assigned to each treatment cannot be determined. Following analysis of caries arrest, blinding can no longer be guaranteed.

Data collection, transmission, and storage

Prior to the beginning of each school year, electronic rosters for each participating school will be provided to study investigators from the DHHS, which will include a unique student identifier, demographic variables, and any available Medicaid identification. School rosters will be used to electronically create personalized informed consent forms for every student in the school, which will then be combined with a letter from the principal explaining the study and distributed to parents of children in each school. Completed informed consent will be collected at the school by study investigators. Schools will be recruited in the first year of the study. Children within schools will be enrolled in each year of the program to accommodate newly registered students each academic year. Recruitment for this study is pending.

Data collected from each participant will be recorded on a password-protected tablet computer using a propriety software system that is pre-populated with the demographic information of the participant from previously obtained DHHS records. Data collectors will be standardized and calibrated prior to study start. Following each data collection day of the study, electronic records will be uploaded to a secure server and stored at the Boston University Data Coordinating Center (DCC) and evaluated for quality assurance. Prior to the transmission of data from the DCC to investigators, identifying

information will be removed and replaced with a unique, anonymized student identifier. This data will be kept at the New York University College of Dentistry on a secure, password-protected server.

Patient and Public Involvement

Planning for this study began over five years ago with pilot studies and meetings with community stakeholders. Stakeholders included representatives from the New Hampshire DHHS Medicaid and Oral Health offices, state dental societies and insurers, community health centers, and a local hospital. The study design was thus informed by stakeholder priorities and preferences, including development of protocols, selection and burden of interventions, training for hygienists, and planned implementation. The design was further created with input from parents of pilot study patients who were participants in group discussions regarding prevention protocols. However, patients themselves were not directly involved.

For this study, parents will be participants in that they will sign informed consent documents. Parents of participating children will also participate in group quarterly and annual meetings. While direct study results will not be disseminated to participants, children will receive a personalized take home message after each clinical visit that summarizes the care they received and the care still needed. Formal study results will be disseminated to community stakeholders.

Sample size calculation

The study is powered for the primary outcomes of caries arrest and prevention. Power calculation for caries arrest assumes a clustered two-group comparison of simple versus complex prevention for a non-inferiority trial. Estimates assume an overall participation rate of 35% across each of the two groups, yielding a total enrollment of 3,926 students within 43 schools. Previous studies of school-based caries prevention in New Hampshire rural elementary schools indicated a baseline caries

prevalence between 30-40%. Assuming an equal allocation of untreated decay across groups of 20% and alpha of 0.05, a total sample size of 198 participants per arm (N=396) would be required for a non-inferiority margin (δ) of caries arrest at 10%, assuming 80% power. When adjusted for within-school clustering (d_{eff} = 10), a sample size of 3,960 is required.

Power for longitudinal analyses of caries prevention was computed for the use of generalized estimating equations [27]. Using the same expected enrollment of 3,926 students, estimates assume an annual attrition rate of 20% and a natural increase in informed consent rates of 10% (which also includes new students entering schools and enrolling in the study) per year. For 95% power, an alpha of 0.05, an average of four observational periods (excluding baseline), a high correlation between repeated observations (r = 0.6), and a design effect of 20, a sample size of 1,961 students per arm is required to detect a difference in uncreated decay of 15% and 2,942 for a difference of 10%.

Statistical Analysis

For the non-inferiority of caries arrest, the per-patient proportion of carious lesions at baseline treated with simple versus complex prevention that stayed arrested throughout the first two years of observation will be determined. Any deciduous teeth with treated carious lesions that are lost due to exfoliation will be considered as arrested throughout the lifetime of the tooth, with arrested caries status being carried over throughout. Thus, tooth-level indicators are able to be present for both primary and permanent dentitions at the same time. With this approach, each carious tooth treated with either simple or comprehensive prevention is a single trial with outcomes either of arrested (1) or failed to arrest (0). The percentage of arrested caries (at the child level) will thus be modeled using multilevel binomial regression with a logit link $Y_j \sim \text{Bin}(\pi_j)$, $E(Y_j) = \pi_j$; where π_j is the probability of success. The noninferiority margin, δ, is set at 10%. While there is no gold standard criterion for the selection of this margin, the margin was set based on collaborative discussion with clinicians to determine what is

considered as clinically unimportant. The null hypothesis is that the experimental treatment (simple prevention) is inferior to the standard treatment (complex prevention) by at least δ: $\pi_{simple} - \pi_{complex} \geq \delta$. The alternative hypothesis is that $\pi_{simple} - \pi_{complex} < \delta$.

Based on results from multilevel binomial models, differences in effect sizes estimated by confidence intervals will be used to determine clinical non-inferiority of the two prevention methods [28]. Confidence intervals will be calculated for the difference between the two interventions, with the width of this interval signifying the extent of noninferiority. If the difference between the two interventions lies to the right of δ, then noninferiority will be concluded. Though this is method is preferred by reporting guidelines, p-values will also be reported, in keeping with other recommendations [28].

For the prevention of new caries, longitudinal data will be analyzed using generalized estimating equations (GEE) and multilevel mixed effects regression models (ML-MEM) with the appropriate error distribution for the prevalence and incidence of untreated caries over time. The number of teeth at risk for each child during each follow-up interval will be identified and the number of those teeth in which new caries is observed at the examination that ends that interval will be determined. Primary teeth lost in each interval and new permanent teeth will not contribute to data for that interval. Data from baseline visits will be omitted from analyses and used as an indicator of any untreated decay at baseline.

To explore non-linear trends in untreated decay between simple and complex prevention, longitudinal data will be analyzed using generalized additive models (GAMs) with non-parametric smoothers, linking the known known proportion $p_{it} = E(y_{it} = 1 | x_{ijt}, z_{it})$ to a nonlinear nonparametric predictor using the link function $n_{it} = g(u_{it}) = \ln(u_{it}/1 - u_{it}) = \sum_{j=1}^{p} s_j(x_{jit}) + z_{it}^T u_i$, where s_j are smooth nonparametric functions and u_i are random effects assumed to be iid ~ $N(0, D(\psi))$ [29]. Heterogeneity and correlation among subjects will be accounted for through random effects.

To compare the cost effectiveness of the two included treatments, empirical results will be incorporated into a Markov decision tree and incremental cost-effectiveness ratios and net health benefits will be estimated. Data for cost and health outcomes will be harvested from trees conducted for short-term (e.g., the follow-up time of the presented clinical trial) and long-term (life course) time horizons. Monte-Carlo simulation based probabilistic sensitivity analyses will be used to detect the probabilities with which the two treatments represent optimum strategies. Finally, budget impact analysis will be applied to estimate expected resource implications on the population level and to determine whether and how potential cost savings could be used to increase population well-being.

Missing data will be adjusted for using multiple imputation and inverse probability weighting (IPW). Statistical analysis will be performed following intention-to-treat and analyzed using Stata v15.0 (StataCorp LLC, College Station, TX, USA) and R v3.1.1.

Ethics and dissemination

Persistent unmet oral health needs in low-income and minority populations stem from an inability to access or afford traditional, office-based dental care. The Institute of Medicine "envisions oral health care in the United States in which everyone has access to quality oral care across the life cycle", which requires a collaborative effort across health systems to eliminate the health barriers contributing to oral diseases and prioritize disease prevention [30]. In response, the Centers for Disease Control and Prevention recommend school-based sealant programs, noting that a large proportion of low-income children do not have access to dental sealants [31]. Simultaneously, the use of silver diamine fluoride to arrest and prevent dental caries is growing [32,33]. Two added benefits to using SDF in school-based prevention programs are that they are faster to provide than sealants and are less costly. Thus, if SDF is shown to be non-inferior to sealants in the arrest and prevention of dental caries, it can be used as an alternative intervention for school-based caries prevention with potentially broader impact.

The direct benefit anticipated for participating children is improved oral health. Due to the minimally invasive nature of experimental interventions, no additional risks are expected. Demonstrating the non-inferiority of SDF to traditional and therapeutic sealants in the arrest and prevention of dental caries in a pragmatic, school-based setting will yield objective data on the practical effectiveness of an efficient, cost-effective caries prevention agent in high-risk populations. Results from testable hypotheses can thus be used to encourage policy change to expand school-based health services to include caries prevention.

Trial Status

Protocol version 1.0 (11/30/17). Recruitment will begin August 2018. Recruitment will be on a rolling, semester-by-semester basis and will conclude June 2023. This trial is registered at www.clinicaltrials.gov (registration #NCT03448107, registered 2/26/2018).

Acknowledgements

The authors would like to thank the patient and stakeholder partners who have assisted in the design and development of this trial.

List of abbreviations

NYU: New York University; SDF: silver diamine fluoride; ITR: interim therapeutic restorations; SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials; DCC: Data Coordinating Center; IPW: inverse probability weighting; GEE: generalized estimating equations; ME-MLM: mixed effects multilevel models; DHHS: Department of Health and Human Services.

Funding

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Availability of data and materials

The datasets generated from this study are available from study investigators upon reasonable request. Results from the proposed study will be presented at national conferences and published in annual reports and peer-reviewed journals.

Authors' contributions

RN and RRR are the study principal investigators. RN and RRR participated in study conception and design and contributed to the writing of the study protocol. RN and RRR drafted and edited the trial protocol. RRR carried out all statistical analyses. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study received approval from the New York University School of Medicine Institutional Review Board (approved October 3, 2017; #i17-00578). All students in participating schools will be invited to participate and parents will sign a consent form after reviewing written information about the study.

Consent for publication

All authors consent to publication of this article.

Competing interests

The authors declare they have no competing interests.

Figure Legend

Figure 1: Schedule of enrolment, interventions, and assessments

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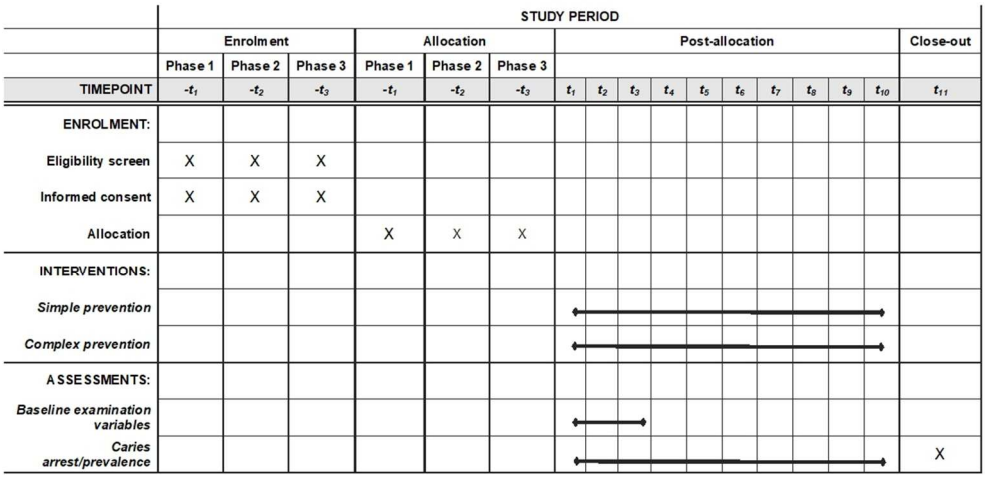

	STUDY PERIOD															
	Enrolment			Allocation			Post-allocation									Close-out
	Phase 1	Phase 2	Phase 3	Phase 1	Phase 2	Phase 3										
TIMEPOINT	$-t_1$	$-t_2$	$-t_3$	$-t_1$	$-t_2$	$-t_3$	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9	t_{10}	t_{11}
ENROLMENT:																	
Eligibility screen	X	X	X														
Informed consent	X	X	X														
Allocation				X	X	X											
INTERVENTIONS:																	
Simple prevention							←	—	—	—	—	—	—	—	—	→	
Complex prevention							←	—	—	—	—	—	—	—	—	→	
ASSESSMENTS:																	
Baseline examination variables							←	—	→								
Caries arrest/prevalence							←	—	—	—	—	—	—	—	—	→	X

97x48mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	14
	2b	All items from the World Health Organization Trial Registration Data Set	14
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig_1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	6 (approved)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	6

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9-10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supp. Files
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	TBD
	13b	For each group, losses and exclusions after randomisation, together with reasons	TBD
Recruitment	14a	Dates defining the periods of recruitment and follow-up	TBD
	14b	Why the trial ended or was stopped	TBD
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	TBD
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	TBD
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	TBD
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	TBD
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	TBD
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	TBD
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	TBD
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	TBD
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	TBD
Other information			
Registration	23	Registration number and name of trial registry	14
Protocol	24	Where the full trial protocol can be accessed, if available	14
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Comparative effectiveness of treatments to prevent dental caries given to rural children in school-based settings: protocol for a cluster randomized controlled trial

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Comparative effectiveness of treatments to prevent dental caries given to rural children in school-based settings: protocol for a cluster randomized controlled trial

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Abstract

Introduction: Dental caries is the most prevalent childhood disease in the world and can lead to infection, pain, and reduced quality of life. Multiple prevention agents are available to arrest and prevent dental caries; however little is known of the comparative effectiveness of combined treatments when applied in pragmatic settings. The aim of the presented study is to compare the benefit of silver diamine fluoride and fluoride varnish versus fluoride varnish and glass ionomer therapeutic sealants in the arrest and prevention of dental caries.

Methods and Analysis: A longitudinal, pragmatic, cluster randomized, single-blind, non-inferiority trial will be conducted in low-income rural children enrolled in public elementary schools in New Hampshire, United States, from 2018-2023. The primary objective is to compare the non-inferiority of alternative agents in the arrest and prevention of dental caries. The secondary objective is to compare cost-effectiveness of both interventions. Caries arrest will be evaluated after two years, and caries prevention will be assessed at the completion of the study. Data analysis will follow intent to treat, and statistical analyses will be conducted using a significance level of 0.05.

Ethics and Dissemination: The standard of care for dental caries is office-based surgery, which presents multiple barriers to care including cost, fear, and geographic isolation. The common intervention used in school-based caries prevention is dental sealants. The simplicity and affordability of silver diamine fluoride may be a viable alternative for the prevention of dental caries in high-risk children. Results can be used to inform policy for best practices in school-based oral health care.

Trial registration: NCT03448107, registered on 2/26/18

Strengths and limitations of this study

- Study is a cluster randomized non-inferiority trial
- Study will compare simple and complex interventions for the treatment and prevention of dental caries measured using standard clinical diagnostic criteria
- Statistical and economic analysis will utilize multilevel modeling, generalized additive modeling, and Markov modeling
- Interventions will be randomly assigned at the school level; any child within each participating school that provides informed consent and assent will receive care twice yearly

Background

Dental caries (tooth decay), a gram positive, aerophilic bacterial infection, is the most prevalent childhood disease in the world, estimated to cause a loss of 3.5 million disability adjusted life years [1,2]. If left untreated, dental caries can lead to acute abscess, sepsis, and in rare circumstances, systemic infection and death [3-5]. Untreated dental caries affects more than 20% of elementary school-aged children in the United States, and over 50% of children have ever experienced caries. Among low-income minority children, caries experience can be greater than 70%, and the prevalence of untreated caries exceeds 30% [6-8]. Though the overall prevalence of caries has reduced over the past ten years, sealant use is lowest among low-income children, and less than half of children from low-income families reported visiting a dentist in the previous year [8-10].

The standard of care for dental caries is office-based surgery consisting of local anesthesia, removal of decay using a dental drill, etching of the tooth with acidic gel, application of an amalgam, composite resin, ionomer, gold, or ceramic material, hardening, and polishing [11]. However, office-based care presents multiple access barriers to patients including cost, fear, and geographic isolation [12]. Fewer than 15% of children who accessed an office-based dentist received preventive care [13], many children do not have access to prevention services [14], and those with the least access to prevention have a higher prevalence of oral disease [14]. As a result, many federal and state organizations and institutions recommend the proactive prevention of caries as an alternative to reactive treatment [14-17]. Caries prevention can be provided through traditional office-based care, mobile dental vans, or as part of a school-based dental program, and the comparative effectiveness of these prevention models has been identified as one of the highest-priority research questions by the Institute of Medicine [18].

Common caries prevention agents include water fluoridation, fluoride toothpaste, fluoride varnish, sealants, interim therapeutic restorations or atraumatic restorations, and silver diamine fluoride

(SDF). Individually, each of these preventive treatments has been shown in randomized clinical trials and systematic reviews to be efficacious in the prevention or treatment of dental caries. A review of thirteen trials in children and adolescents found that those treated with fluoride varnish experienced an average reduction of decayed, missing, or filled tooth surfaces of 43% when compared to untreated youth [19]. A systematic review of six trials showed that resin-based sealants significantly reduced the risk of caries in permanent molars up to 48 months compared to no sealants, and estimated that if 70% of control unsealed tooth surfaces were decayed, application of a resin-based sealant would significantly reduce the proportion of carious surfaces to under 19% [20]. Further, there was not sufficient evidence in both systematic reviews and meta-analyses to suggest the superiority of the preventive effects of either resin-based or glass-ionomer sealant material [20,21]. A 2012 meta-analysis of 29 studies indicated that pits and fissures of teeth sealed with interim therapeutic restorations had a mean annual caries incidence over three years of only one percent [22]. Finally, silver diamine fluoride has been shown in reviews to have higher preventive fractions of arrested and prevented caries than fluoride varnish [23], and SDF at 38% concentration applied biannually was more effective in preventing caries than annual applications of lower concentrations [24].

Despite this evidence, the combined effectiveness of different treatments, as well as their feasibility for use in pragmatic settings, is unknown. The objectives of the presented longitudinal, pragmatic, cluster randomized, single-blind, non-inferiority trial are to compare the clinical and cost effectiveness of a simple prevention package (consisting of fluoride varnish and SDF) versus a complex prevention package (consisting of fluoride varnish and therapeutic sealants) in the arrest and prevention of dental caries among low-income rural children in primary school settings. It is hypothesized that simple caries prevention is non-inferior to complex care and is more cost-effective for large-scale implementation.

Methods/Design

This is a longitudinal, pragmatic, cluster randomized, single-blind, non-inferiority clinical trial comparing silver diamine fluoride with fluoride varnish versus therapeutic sealants with fluoride varnish given biannually to children enrolled in public elementary schools in New Hampshire. Prior to the study start, participating schools meeting inclusion criteria will be randomly assigned to receive fluoride varnish/SDF or fluoride varnish/sealants in six-month intervals (±1 month). At each observational period, study participants with informed consent will receive a comprehensive oral examination provided by a licensed dental hygienist (Figure 1) [25,26]. The clinical examination will include an assessment of every tooth and tooth surface for decayed, filled, or missing teeth, as well as pulpal involvement or abscess. Following the oral evaluation, participants will receive the assigned treatments. Any participant presenting with a medical emergency will be referred to school nurses for follow-up care.

This trial protocol is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and has received approval from the New York University School of Medicine Institutional Review Board (#i17-01221). Any changes to the study protocol will be communicated to the IRB and funder in quarterly reports, and investigators will cooperate with any independent audit on behalf of the IRB or funding organization. The study was registered at www.clinicaltrials.gov (#NCT03448107).

Treatment description and regimen

Simple Prevention. One drop (0.05 ml) of silver diamine fluoride (Advantage Arrest ™) solution at 38% concentration (2.24 F-ion mg/dose) will be dispensed per child. Posterior tooth surfaces to be treated will be dried, after which the SDF will be applied with a microbrush to all asymptomatic carious lesions and to all pits and fissures on bicuspids and molar teeth for thirty seconds. Fluoride varnish (5%

NaF) will then be applied to all teeth. Simple prevention will be provided by either dental hygienists or registered nurses.

Complex Prevention. All primary and permanent teeth will be dried prior to application. Pits and fissures on all bicuspids and molar teeth will be sealed with glass ionomer sealants (GC Fuji IX). Glass ionomer sealants (interim therapeutic restorations) will also be placed on all asymptomatic carious lesions. Fluoride varnish (5% NaF) will then be applied to all teeth. Complex prevention will be provided by dental hygienists.

Both arms will also receive toothbrushes, fluoride toothpaste, and oral hygiene instruction. Clinical care will be provided in a dedicated room in each school using mobile equipment and disposable supplies.

Risks and Adverse Events

Each intervention used in this trial is currently employed in clinical practice as a standard of care procedure. The potential risks for study participants are minimal and identical to the risk for children obtaining care in a dental office. The greatest risk is an allergic reaction to fluoride varnish, silver diamine fluoride, or glass ionomer. All adverse events occurring during the study period will be recorded: at each contact with the study participant, investigators will seek information on adverse events by specific questions and an oral examination. Evidence of adverse events will be recorded on electronic health records and appropriate case report forms. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that participation in the study was not the cause. Serious adverse events ongoing at study end will be followed to determine the final outcome. Adverse event reports will be reported to the IRB within five working days from the time investigators become aware of the event.

Definition of outcome measures

Primary outcome measures. Primary outcomes include clinically-evaluated caries arrest and the prevention of new caries. Caries arrest will be evaluated after two years and the prevalence of new caries will be evaluated after five years.

Secondary outcome measures. Secondary outcomes include the comparative cost effectiveness of simple versus complex prevention in the arrest and prevention of dental caries.

Recruitment & Eligibility

In collaboration with the New Hampshire Department of Health and Human Services (DHHS), study investigators identified extant school-based caries prevention programs currently operating in rural counties in New Hampshire. Program officials were contacted to solicit interest in participating in the proposed study. Program officials, in turn, contacted school principals to determine interest in participation. Each participating program and school has confirmed written consent for the study.

Inclusion Criteria. Any existing caries prevention program operating in rural (defined using criteria from the U.S. Department of Agriculture) areas, with official Title 1 status, and located in a health professional shortage area was eligible to participate. All schools within eligible programs were eligible to participate.

Randomization

Participating schools will be block randomized at the school level to receive either the simple or complex treatment using a random number generator. Study statisticians will generate random numbers and assign schools to each number sequence.

Blinding

Due to the nature of the treatments provided, dental hygienists providing care will not be independent from study protocols and therefore are not blinded. Assignment to treatments will follow a predetermined randomization list at the school level, and all students with consent in participating schools will receive the assigned treatment. However, all data analyses for caries arrest will be blinded, as data will be masked prior to analysis such that which schools were assigned to each treatment cannot be determined. Following analysis of caries arrest, blinding can no longer be guaranteed.

Data collection, transmission, and storage

Prior to the beginning of each school year, electronic rosters for each participating school will be provided to study investigators from the DHHS, which will include a unique student identifier, demographic variables, and any available Medicaid identification. School rosters will be used to electronically create personalized informed consent forms for every student in the school, which will then be combined with a letter from the principal explaining the study and distributed to parents of children in each school. Completed informed consent will be collected at the school by study investigators. Schools will be recruited in the first year of the study. Children within schools will be enrolled in each year of the program to accommodate newly registered students each academic year. Recruitment for this study is pending.

Data collected from each participant will be recorded on a password-protected tablet computer using a propriety software system that is pre-populated with the demographic information of the participant from previously obtained DHHS records. Data collectors will be standardized and calibrated prior to study start. Following each data collection day of the study, electronic records will be uploaded to a secure server and stored at the Boston University Data Coordinating Center (DCC) and evaluated for quality assurance. Prior to the transmission of data from the DCC to investigators, identifying

information will be removed and replaced with a unique, anonymized student identifier. This data will be kept at the New York University College of Dentistry on a secure, password-protected server.

Patient and Public Involvement

Planning for this study began over five years ago with pilot studies and meetings with community stakeholders. Stakeholders included representatives from the New Hampshire DHHS Medicaid and Oral Health offices, state dental societies and insurers, community health centers, and a local hospital. The study design was thus informed by stakeholder priorities and preferences, including development of protocols, selection and burden of interventions, training for hygienists, and planned implementation. The design was further created with input from parents of pilot study patients who were participants in group discussions regarding prevention protocols. However, patients themselves were not directly involved.

For this study, parents will be participants in that they will sign informed consent documents. Parents of participating children will also participate in group quarterly and annual meetings. While direct study results will not be disseminated to participants, children will receive a personalized take home message after each clinical visit that summarizes the care they received and the care still needed. Formal study results will be disseminated to community stakeholders.

Sample size calculation

The study is powered for the primary outcomes of caries arrest and prevention. Power calculation for caries arrest assumes a clustered two-group comparison of simple versus complex prevention for a non-inferiority trial. Estimates assume an overall participation rate of 35% across each of the two groups, yielding a total enrollment of 3,926 students within 43 schools. Previous studies of school-based caries prevention in New Hampshire rural elementary schools indicated a baseline caries

prevalence between 30-40%. Assuming an equal allocation of untreated decay across groups of 20% and alpha of 0.05, a total sample size of 198 participants per arm (N=396) would be required for a non-inferiority margin (δ) of caries arrest at 10%, assuming 80% power. When adjusted for within-school clustering (d_{eff} = 10), a sample size of 3,960 is required.

Power for longitudinal analyses of caries prevention was computed for the use of generalized estimating equations [27]. Using the same expected enrollment of 3,926 students, estimates assume an annual attrition rate of 20% and a natural increase in informed consent rates of 10% (which also includes new students entering schools and enrolling in the study) per year. For 95% power, an alpha of 0.05, an average of four observational periods (excluding baseline), a high correlation between repeated observations (r = 0.6), and a design effect of 20, a sample size of 1,961 students per arm is required to detect a difference in uncreated decay of 15% and 2,942 for a difference of 10%.

Statistical Analysis

For the non-inferiority of caries arrest, the per-patient proportion of carious lesions at baseline treated with simple versus complex prevention that stayed arrested throughout the first two years of observation will be determined. Any deciduous teeth with treated carious lesions that are lost due to exfoliation will be considered as arrested throughout the lifetime of the tooth, with arrested caries status being carried over throughout. Thus, tooth-level indicators are able to be present for both primary and permanent dentitions at the same time. With this approach, each carious tooth treated with either simple or comprehensive prevention is a single trial with outcomes either of arrested (1) or failed to arrest (0). The percentage of arrested caries (at the child level) will thus be modeled using multilevel binomial regression with a logit link $Y_j \sim \text{Bin}(\pi_j)$, $E(Y_j) = \pi_j$; where π_j is the probability of success. The noninferiority margin, δ, is set at 10%. While there is no gold standard criterion for the selection of this margin, the margin was set based on collaborative discussion with clinicians to determine what is

considered as clinically unimportant. The null hypothesis is that the experimental treatment (simple prevention) is inferior to the standard treatment (complex prevention) by at least δ: $\pi_{simple} - \pi_{complex} \geq \delta$. The alternative hypothesis is that $\pi_{simple} - \pi_{complex} < \delta$.

Based on results from multilevel binomial models, differences in effect sizes estimated by confidence intervals will be used to determine clinical non-inferiority of the two prevention methods [28]. Confidence intervals will be calculated for the difference between the two interventions, with the width of this interval signifying the extent of noninferiority. If the difference between the two interventions lies to the right of δ, then noninferiority will be concluded. Though this is method is preferred by reporting guidelines, p-values will also be reported, in keeping with other recommendations [28].

For the prevention of new caries, longitudinal data will be analyzed using generalized estimating equations (GEE) and multilevel mixed effects regression models (ML-MEM) with the appropriate error distribution for the prevalence and incidence of untreated caries over time. The number of teeth at risk for each child during each follow-up interval will be identified and the number of those teeth in which new caries is observed at the examination that ends that interval will be determined. Primary teeth lost in each interval and new permanent teeth will not contribute to data for that interval. Data from baseline visits will be omitted from analyses and used as an indicator of any untreated decay at baseline.

To explore non-linear trends in untreated decay between simple and complex prevention, longitudinal data will be analyzed using generalized additive models (GAMs) with non-parametric smoothers, linking the known known proportion $p_{it} = E(y_{it} = 1 | x_{ijt}, z_{it})$ to a nonlinear nonparametric predictor using the link function $n_{it} = g(u_{it}) = \ln(u_{it}/1 - u_{it}) = \sum_{j=1}^{p} s_j(x_{jit}) + z_{it}^T u_i$, where s_j are smooth nonparametric functions and u_i are random effects assumed to be iid ~ $N(0, D(\psi))$ [29]. Heterogeneity and correlation among subjects will be accounted for through random effects.

To compare the cost effectiveness of the two included treatments, empirical results will be incorporated into a Markov decision tree and incremental cost-effectiveness ratios and net health benefits will be estimated. Data for cost and health outcomes will be harvested from trees conducted for short-term (e.g., the follow-up time of the presented clinical trial) and long-term (life course) time horizons. Monte-Carlo simulation based probabilistic sensitivity analyses will be used to detect the probabilities with which the two treatments represent optimum strategies. Finally, budget impact analysis will be applied to estimate expected resource implications on the population level and to determine whether and how potential cost savings could be used to increase population well-being.

Missing data will be adjusted for using multiple imputation and inverse probability weighting (IPW). Statistical analysis will be performed following intention-to-treat and analyzed using Stata v15.0 (StataCorp LLC, College Station, TX, USA) and R v3.1.1.

Ethics and dissemination

Persistent unmet oral health needs in low-income and minority populations stem from an inability to access or afford traditional, office-based dental care. The Institute of Medicine "envisions oral health care in the United States in which everyone has access to quality oral care across the life cycle", which requires a collaborative effort across health systems to eliminate the health barriers contributing to oral diseases and prioritize disease prevention [30]. In response, the Centers for Disease Control and Prevention recommend school-based sealant programs, noting that a large proportion of low-income children do not have access to dental sealants [31]. Simultaneously, the use of silver diamine fluoride to arrest and prevent dental caries is growing [32,33]. Two added benefits to using SDF in school-based prevention programs are that they are faster to provide than sealants and are less costly. Thus, if SDF is shown to be non-inferior to sealants in the arrest and prevention of dental caries, it can be used as an alternative intervention for school-based caries prevention with potentially broader impact.

The direct benefit anticipated for participating children is improved oral health. Due to the minimally invasive nature of experimental interventions, no additional risks are expected. Demonstrating the non-inferiority of SDF to traditional and therapeutic sealants in the arrest and prevention of dental caries in a pragmatic, school-based setting will yield objective data on the practical effectiveness of an efficient, cost-effective caries prevention agent in high-risk populations. Results from testable hypotheses can thus be used to encourage policy change to expand school-based health services to include caries prevention.

Trial Status

Protocol version 1.0 (11/30/17). Recruitment will begin August 2018. Recruitment will be on a rolling, semester-by-semester basis and will conclude June 2023. This trial is registered at www.clinicaltrials.gov (registration #NCT03448107, registered 2/26/2018).

Acknowledgements

The authors would like to thank the patient and stakeholder partners who have assisted in the design and development of this trial.

List of abbreviations

NYU: New York University; SDF: silver diamine fluoride; ITR: interim therapeutic restorations; SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials; DCC: Data Coordinating Center; IPW: inverse probability weighting; GEE: generalized estimating equations; ME-MLM: mixed effects multilevel models; DHHS: Department of Health and Human Services.

Funding

This work is supported by the National Institute on Minority Health and Health Disparities (#R01MD011526; Niederman & Ruff, Principal Investigators).

Availability of data and materials

The datasets generated from this study are available from study investigators upon reasonable request. Results from the proposed study will be presented at national conferences and published in annual reports and peer-reviewed journals.

Authors' contributions

RN and RRR are the study principal investigators. RN and RRR participated in study conception and design and contributed to the writing of the study protocol. RN and RRR drafted and edited the trial protocol. RRR carried out all statistical analyses. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study received approval from the New York University School of Medicine Institutional Review Board (approved October 3, 2017; #i17-00578). All students in participating schools will be invited to participate and parents will sign a consent form after reviewing written information about the study.

Consent for publication

All authors consent to publication of this article.

Competing interests

The authors declare they have no competing interests.

Figure Legend

Figure 1: Schedule of enrolment, interventions, and assessments

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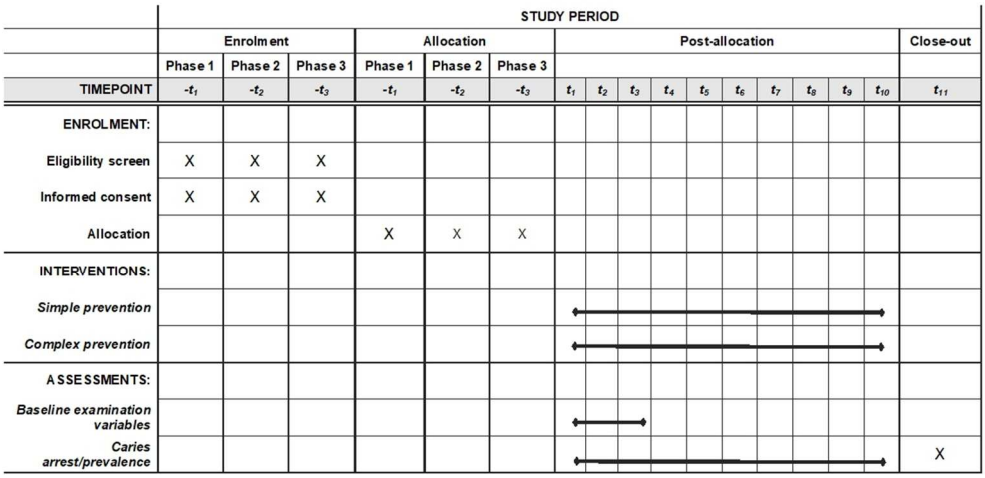

	STUDY PERIOD															
	Enrolment			Allocation			Post-allocation									Close-out
	Phase 1	Phase 2	Phase 3	Phase 1	Phase 2	Phase 3										
TIMEPOINT	$-t_1$	$-t_2$	$-t_3$	$-t_1$	$-t_2$	$-t_3$	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9	t_{10}	t_{11}
ENROLMENT:																	
Eligibility screen	X	X	X														
Informed consent	X	X	X														
Allocation				X	X	X											
INTERVENTIONS:																	
Simple prevention							←	—	—	—	—	—	—	—	—	→	
Complex prevention							←	—	—	—	—	—	—	—	—	→	
ASSESSMENTS:																	
Baseline examination variables							←	—	→								
Caries arrest/prevalence							←	—	—	—	—	—	—	—	—	→	X

97x48mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	14
	2b	All items from the World Health Organization Trial Registration Data Set	14
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig_1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	6 (approved)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	6

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9-10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supp. Files
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10-12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	TBD
	13b	For each group, losses and exclusions after randomisation, together with reasons	TBD
Recruitment	14a	Dates defining the periods of recruitment and follow-up	TBD
	14b	Why the trial ended or was stopped	TBD
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	TBD
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	TBD
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	TBD
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	TBD
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	TBD
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	TBD
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	TBD
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	TBD
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	TBD
Other information			
Registration	23	Registration number and name of trial registry	14
Protocol	24	Where the full trial protocol can be accessed, if available	14
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.