FOR USE FOR A CLINICAL TRIAL OF A NON-DRUG/DEVICE INTERVENTION
NOTE: It is not necessary to follow this protocol outline exactly as long as the key elements described below are included as appropriate to the study design.

Comparative Effectiveness of School-Based Caries Prevention Programs for Children in Underserved, Low Income, Hispanic Communities

This is a New York City elementary school-based, pragmatic, cluster, randomized controlled, non-inferiority trial comparing simple vs complex caries prevention. Simple is defined as fluoride varnish + silver diamine fluoride. Complex is defined as fluoride varnish + traditional sealants + therapeutic sealants. All interventions are: currently used in clinical practice; have American Dental Association billing codes; and, depending on the state and third party administrator, and are compensated by Medicaid.

Principal Investigator:	Richard Niederman Department of Epidemiology & Health Promotion 433 First Avenue, Room 720 212-998-9719 rniederman@nyu.edu Ryan Richard Ruff Department of Epidemiology & Health Promotion 433 First Avenue, Room 712 212-998-9663 ryan.ruff@nyu.edu
Funding Support:	Patient Centered Outcomes Research Institute 1828 L St., NW, Suite 900 Washington, DC 20036 Phone: (202) 827-7700 Fax: (202) 355-9558
Study Intervention:	The trial compares two caries prevention protocols delivered twice yearly in elementary schools: a novel simple intervention of fluoride varnish + silver diamine fluoride vs the traditional complex intervention of fluoride varnish + traditional sealants + therapeutic sealants.
IRB Number:	*Insert IRB Number for Protocol*

Initial version: April 19, 2017
Amended: date
Amended: date

Table of Contents

List of Abbreviations

NYU: New York University;
SDF: silver diamine fluoride;
ITR: interim therapeutic restorations;
COHIP-SF: Child Oral Health Impact Profile (Short Form);
NYC: New York City;
DOE: Department of Education;
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.

Study Summary

Title	Comparative Effectiveness of School-Based Caries Prevention Programs for Children in Underserved, Low Income, Hispanic Communities
Short Title	School-based Caries Prevention
IRB Number	S17-00578
Study Type	Human
Study Design	Pragmatic, cluster, randomized controlled, non-inferiority trial
Study Intervention	Simple prevention (fluoride varnish + silver diamine fluoride) vs complex prevention (fluoride varnish + traditional sealants + therapeutic sealants)
Study Duration	5 years
Study Location(s)	New York City Title 1 Elementary Schools
Primary Objective	To determine if the newer simple caries prevention is not inferior to the traditional complex caries prevention.
Sample Size	60 schools (approximately 15,000 children)
Diagnosis and Main Inclusion Criteria	The disease/condition is untreated caries. All children in the participating schools with informed consent will be included. The only exclusion criteria are children not in the participating schools, and children without informed consent.
Control / Comparison	The new simple prevention will be compared to the traditional complex prevention.
Statistical Methodology	Primary outcomes include caries arrest, caries prevention, and quality of life. We will assess these using multilevel binomial regression and generalized estimating equations.

1 Introduction

This study will be conducted in compliance with the protocol approved by the IRB, GCP guidelines, and applicable NYUMC and federal regulatory requirements.

1.1 Background

Caries Epidemiology, Current Standards of Care, and Limitations

Caries is the globe's and U.S.'s most prevalent, uncontrolled, preventable bacterial infection[1].

More than 50% of U.S. elementary school-age children have experienced caries (tooth decay or cavities), and more than 20% have untreated caries. For Hispanic/Latino, low-income children caries experience is over 70% and the untreated caries is over 30%[2-4]. Even more problematic, children with untreated caries have an incidence of sepsis ranging from 5% to 10%[5]. In rare instances, untreated decay can lead to serious systemic infections and even death [6].

Disease Burden in New York City. Children's oral health needs, and particularly Hispanic/Latino children from low income families, exceed U.S. averages[7-9]. Current estimates indicate that 38% have untreated caries, 2/3 do not have sealants, and all have difficulty accessing care.

Pathophysiology and Diagnosis. Caries is a Gram +, aerophilic bacterial infection. These bacteria reside on tooth surfaces and release acid as a result of their metabolic activity. The acids, essentially, etch the tooth surface. If left untreated, the bacterial ultimately create a crater or cavity in the tooth surface. The primary diagnostic method for caries is visual/tactile. That is, visually assessing a tooth surface with a light and mirror, and exploring the tooth surface with a blunt probe.

The Current "Standard of Care" and Limitations. Office-based surgical care ("anesthesia, drilling and filling") is standard of care[10]. However, these fillings are not permanent: they have a limited life span of ~10 years and then require replacement by a larger restoration[11-13]. The net result is that fillings, once placed, must be repeated with more extensive and expensive restorations[14,15]. Office-based care, and particularly surgical care, presents multiple access barriers for patients including, in decreasing order of patient importance: cost, fear, geographic location/travel, time, knowledge, culture and literacy [16-19].

Effective Caries Prevention is Available and Cost Effective. Systematic reviews verify the efficacy for numerous caries preventing agents (Table 1)[20]. The identified systematic reviews examined trials of individual agents. Our work, demonstrates that, when used in combination, and delivered by dental hygienists in schools, complex preventive care can be effective in reducing the prevalence/incidence of caries[21,22].

Table 1. Summary of Caries Preventive Systematic Reviews[20]

Agent	Frequency	Est. % Efficacy
1. Water Fluoridation	Continuous	20-40[1]
2. Fluoride toothpaste	2X/day	25[2]
3. Fluoride varnish	More than 2X/year	45[3]
4. Traditional Sealant	1X /pits & fissures	80[4]
5. Therapeutic Sealant*	1x/ caries	80[5]
6. Silver-diamine-fluoride	2X/year	80[6]

References: 1. [23-26]; 2. [27,28]; 3. [29]; 4. [30-32]; 5. [30,33-35]; 6. [36-38]. * Seal caries to prevent further tooth destruction. Requires no anesthesia or drilling. Also called: Interim Therapeutic, Atraumatic, or Temporary Restorations, Minimal Intervention Dentistry. ** CHW: Community health worker

Systematic reviews with economic assessments indicate that: 1) caries prevention is cost-effective[39-41]; and 2) investment in prevention outweighs investment in fillings[33,41-44]. Further, when compared to traditional fillings: 3) therapeutic sealants require no excision of tooth structure and have significantly fewer adverse events such as acute pain and endodontic involvement [33,35].

A New Standard of Care with Limitations[45]. While effective caries prevention agents are available most dental offices do not provide them. From 2003-2009, fewer than 15% of children who accessed

office-based dental care received appropriate preventive care (e.g.: topical fluoride or sealants[46]), and in 2013, fewer than 16% of 6-9 year olds received sealants[47]. Further, fewer than 40% of U.S. dentists provide sealants[48]. In NYC, for children 6-12, 65% of children have never had sealants, and for children who have seen a dentist 60% were not given sealants[7].

To overcome the barriers of office-based care, at least 13 reports[49], and multiple federal agencies recommend prevention, and in particular, school-based caries prevention[50-52]. These same reports also recognize the gap between knowing how to implement prevention in a community settings to demonstrate effectiveness[14,15,17,53,54]. Two national surveys[55,56] and our insurance analysis confirms this[57].

Intervention Summary

We propose comparing the effectiveness of two caries prevention protocols – one a newer, simpler protocol and the other an older, more complex protocol that we've previously implemented[58]. To increase access we are proposing to bring preventive care to children, rather than children to preventive care[59].

Prevention Summary. As indicated in the table below, both simple and complex prevention provide primary and secondary prevention. Based on systematic reviews of human randomized controlled trials (see Table 1), fluoride varnish + silver diamine fluoride, when compared to fluoride varnish + traditional sealants + therapeutic sealants provide approximately the same efficacy. Further, both preventive arms have fewer adverse events than classical restorative care[33,35]. From these perspectives, the current office-based surgical care model is a clinical example of the over-use of ineffective therapy, and the under-use of effective prevention[20,57,60-63].

However, silver diamine fluoride was only approved for U.S. use in 2014. Therefore, based on educational training and clinical practice experience, the historical bias is that complex prevention (fluoride vanish + traditional sealants + therapeutic sealants) will be more effective than simple prevention (fluoride varnish + silver diamine fluoride). We propose testing this hypothesis. We therefore propose a definitive study examining the effectiveness of community-based prevention.[57,59]

Table 2. Definitions of Primary and Secondary Prevention: Comparison of Proposed Prevention Protocols*

		Simple Prevention		Complex Prevention		
Terminology	**Goal**	**F-Varnish**	**SDF**	**F-Varnish**	**Sealant**	**TS**
Primary Prevention	Smooth surface prevention	+ (45%)		+ (45%)		
	Pits and fissure prevention		+ (80%)		+(80%)	
SecondaryPrevention	Caries arrest		+ (80%)			+ (80%)

* Percentages are efficacy estimates from systematic reviews of human randomized controlled trials.
SDF = silver-diamine-fluoride. Sealant = traditional sealant. TS = therapeutic sealant

1.2 Study Rationale

Rationale for Study Population. To most rapidly provide and demonstrate improved health equity, in collaboration with the NYC Department of Education and the Department of Health and Mental Hygiene, we selected the highest need, low-income, minority community, with the lowest access to care - Hispanic/Latino elementary school children, living in the Bronx. The median household income is $34.3k and the highest Hispanic/Latino population in the NY state (55.1% of 1.46m people)[64].

According to the NY City Department of Education data: 1) There are 99 Bronx elementary schools (grades PK to 8) with a preponderance of Hispanic/Latino children (average 69% per school; range: 51% to 90%). 2) The total enrollment in these schools is 53,089 (average 596 per school; range: 84 to 1705). 3) Almost 95% of these students come from families at or below 138% of the federal poverty level, and 60% of the children are current Medicaid participants.

In addition to the 99 Bronx elementary schools, there are 68 elementary schools serving 34,762 children with similar demographics in Manhattan, Queens, Brooklyn, and Staten Island[65]. More broadly, of

the approximately 1,800 NY City public schools serving 1.1m children, almost 1,000 schools serve some 800,000 children from low-income families (<138% of the federal poverty level)[66].

Benefits of Study Results and Relevance to Policies and Priorities. There are three distinct benefits. First, simple prevention takes approximately ¼ the time and ¼ the cost of complex prevention. Concretely: simple takes ~5 minutes and costs ~$20 (supplies + personnel), while complex takes ~20 minutes and costs ~$80 (supplies + personnel). Therefore, if simple is not inferior, its use will increase access to effective care. Second, the preventive agents are grouped to provide both primary and secondary prevention. Third, the methods to be applied and the outcomes identified both address national Healthy People 2020 goals.

Known and Potential Risks and Benefits. Caries prevention using: silver nitrate is more than 100 years old; fluoride is more than 50 years old; while sealants and silver diamine fluoride are more than 25 years old. The only known risks are misuse of the materials (e.g.: patient swallowing). The potential risks are allergic reaction to either the fluoride or the silver or the glass ionomer sealants. We only able to identify 2 case reports of an allergic reaction to fluoride varnish, and these were prior to the current formulations.

The benefit to all participants is that they will receive primary and secondary caries prevention twice yearly.

2 Study Objectives

2.1 Primary Objective.

To determine if simple prevention is non-inferior to complex prevention for caries arrest and longitudinal caries prevention.

2.2 Secondary Objective(s)

To determine if children receiving either simple prevention or complex prevention will have improved quality of life, reduced school absence, and higher academic performance when compared to matched students in non-participating schools

3 Study Design

3.1 General Design

This is an elementary school-based, pragmatic, cluster, randomized controlled trial comparing the clinical effectiveness of two caries prevention protocols that both provide primary and secondary prevention. The two interventions and the efficacy of each element are provided in Table 2 above. Care will be provided twice yearly to mirror health care recommendations in private practice.

The trial will last 5 years to provide outcome measures of caries arrest at 1 year and caries prevention at 3 years. Care will continue to be provided after termination of the trial.

Children will be enrolled at the beginning of each school year.

3.2 Primary Study Endpoints

Caries arrest and prevention will be determined at each visit. The primary end point for caries arrest will be at 1 year, and follow on to termination of trial determine the length of time that caries remains arrested. The primary end point for caries prevention will be at 3 years, and follow on to termination of trial to determine stability of prevention.

Presence / absence of caries is assessed by visual/tactile methods. Sound tooth surfaces appear white and smooth. Active caries appear brown and soft. Arrested caries appear dark brown or black and hard.

For clinical assessment, we will train and standardize clinicians using validated criteria implemented by the Centers for Disease Control and Prevention (CDC) in the National Health and

Nutrition Examination Surveys (NHANES). Training and validation were developed and documented by our CoI, Dr. Beltran, while at the CDC and field tested in the examination of special athletes[67,68]. Training and standardization of these examiners implement the World Health Organization guidelines[69,70].

3.3 Secondary Study Endpoints

School absence and academic performance will be provided by the NYC Department of Education.

3.4 Primary Safety Endpoints

The care provided is usual and customary care, not high-risk. The only risk about which we are aware is a toothache. Our history suggests that this occurs in approximately 1 in 2000 children. In our experience, this occurrence is far less than the percentage of children with tooth aches prior to initiation of prevention (approximately 5 in 100 children).

4 Participant Selection, Enrollment, and Withdrawal

4.1 Study Population

The study population are elementary school children attending NYC schools. More specifically, we are focusing on schools serving low-income minority populations. The New York City Department of Education indicated that the largest low-income minority population are Latino/Hispanic children.

We therefore selected the Bronx as an initial focus, because it is the lowest-income county in NY state, with a median household income of $34.3k and the highest Hispanic/Latino population in the NY state (55.1% of 1.46m people)[64].

According to the NY City Department of Education data: 1) There are 99 Bronx elementary schools (grades PK to 8) with a preponderance of Hispanic/Latino children (average 69% per school; range: 51% to 90%). 2) The total enrollment in these schools is 53,089 (average 596 per school; range: 84 to 1705). 3) Almost 95% of these students come from families at or below 138% of the federal poverty level, and 60% of the children are current Medicaid participants.

In addition to the 99 Bronx elementary schools, there are 68 elementary schools serving 34,762 children with similar demographics in Manhattan, Queens, Brooklyn, and Staten Island[65]. More broadly, of the approximately 1,800 NY City public schools serving 1.1m children, almost 1,000 schools serve some 800,000 children from low-income families (<138% of the federal poverty level)[66].

4.2 Inclusion Criteria

All children attending a participating school, with informed consent and assent, will receive care, independent of race, ethnicity, sex, medical condition, or ability to pay. Children with informed consent can join at any time.

4.3 Exclusion Criteria

The only excluded children will be those: (1) not attending participating schools, (2) those attending participating schools without informed consent, or (3) those attending participating schools with informed consent, but without assent.

4.4 Participant Recruitment, Screening and Enrollment

School Solicitation. To identify school participants, any primary school in New York City that had a Hispanic student population ≥50% and had at least 80% of the student population participating in free or reduced lunch (“Title 1 schools”) was eligible to participate. The NYC Department of Education solicited every school meeting the above criteria. Excluded from the solicitation were schools with an existing school-based dental health program (e.g., sealant programs). School principals were sent letters

describing the study protocol and interventions, and any interested principal opted into the program. NYC Department of Education identified 30 schools for participation in YR 01, and will solicit and identify another 30 for YR 02.

School Randomization. Participating schools will be randomized to receive either simple or complex prevention. All children in a given school, with informed consent, will receive the same preventive care twice per year during the progress of this program.

School Rosters and Informed Consent Preparation. In August the NYC Department of Education will provide an electronic roster for each school. The rosters include the student's unique identifier, name, address, phone, date of birth and sex, home language, race/ethnicity, free/reduced lunch participation, grade and teacher, as well as the Medicaid number, if available. The rosters are used to create personalized informed consent by school, grade, teacher, and student. The informed consent are electronically combined with a letter from the principal, personalized for the child, explaining the program. A single PDF is created for each school. These are printed at NYU. These forms have bar codes and are electronically readable.

Informed Consent. The NYU team will work with each school to schedule informed consent delivery, and coordinate distribution with other school forms at the beginning of the school year. NYU will also schedule form retrieval, and then securely scan the signed informed consents to the data coordinating center. This information then populates the master data base and the electronic dental record on iPads. This process is repeated yearly. Reconciliation of the school roster and informed consent facilitates assessment of participation by school, grade, and teacher.

4.5 Early Withdrawal of Participants

A parent may withdraw their child at any time for any reason, with either a written request or a phone call (with verification) to the PI, CRA, or school. Upon withdrawal the data coordinating center is notified, and the record flagged to remove the child from the informed consent list in the data base and the iPad electronic record. Students who withdraw are not replaced.

5 Study Intervention

5.1 Description

Examination. The NYU team will work with each school for scheduling care delivery, and school space to deliver care, and then coordinate care delivery.

Each program will use password-protected iPads with electronic dental records pre-populated with demographic information of all students with informed consent. Student lists on the iPads will be used to: collect students during the care delivery days; record clinical findings and care delivered; and generate take home forms (see below). On the scheduled care days we will provide toothbrush prophylaxis, oral hygiene instruction, a toothbrush and fluoridated toothpaste. We will also carry out an examination and provide preventive care.

The examination will include a soft tissue inspection and an assessment of all primary and permanent teeth to determine the presence/ absence of decay (active or arrested), missing, filled, or sealed surfaces on all teeth.

Prevention. Both simple and complex care regimens provide both primary and secondary caries prevention. The goal of primary prevention is to prevent or delay the initial carious lesion using: 1) fluoride varnish for smooth surfaces (simple and complex prevention); and 2) either silver diamine fluoride (simple prevention) or sealants (complex prevention) for pits and fissures. The goal of secondary prevention is to arrest caries *in situ*, and prevent disease progression. This is accomplished with silver diamine fluoride (simple prevention) or therapeutic sealants (complex prevention).

Take Home Messages and Follow-on Care. We will provide two take-home messages, one each for parents, school nurses. The parents' message will highlight the care provided, additional care needed, and names of a local dentist and community health centers that can provide follow on care. The message for the nurses will be Excel spreadsheets that list the children seen, care provided and care

needed, and that identify children who need immediate care. For the latter, we will follow each school's protocol.

5.2 Study Administration and Duration

Care is delivered in a school room (e.g.: class room, nurse office, library, etc) using mobile equipment and disposable supplies. These are set up prior to the beginning of the school day. Care is delivered only during school hours.

Based on informed consents, children are collected in groups of 5 or 6 from a class room and escorted to the clinical room. The clinician is either a dental hygienist or a nurse, with an assistant recording the examination and care delivery.

Simple prevention (examination and care) takes approximately 5 minutes. It consists or a tooth brush cleaning, oral hygiene instruction, an examination, delivery of silver diamine fluoride using a microbrush to all pits and fissures on bicuspids or molar teeth, and to all carious lesions. Fluoride varnish is then applied. Each child is given a small bag with a toothbrush, fluoride toothpaste, and a note indicating the results of the examination, the care provided, and a list of local dentists or community health centers for follow on care.

Complex prevention (examination and care) takes approximately 20 minutes. It consists or a tooth brush cleaning, oral hygiene instruction, an examination, delivery of glass ionomer sealants to all pits and fissures on bicuspids or molar teeth, and to all carious lesions. Fluoride varnish is then applied. Each child is given a small bag with a toothbrush, fluoride toothpaste, and a note indicating the results of the examination, the care provided, and a list of local dentists or community health centers for follow on care.

Examination and care is provided twice yearly.

5.3 Control/Comparison Group and Confounding Factors

Complex prevention is the "comparison" while simple prevention is the "intervention" group. Both groups receive primary and secondary prevention and we expect both protocols to be similarly effective in reducing untreated caries.

We will include relevant confounders a priori in our analysis, including: gender, previous (or concurrent) dental treatment (identified as new or existing treated dentition at examination), age at examination, race/ethnicity, and any school-level indicators. As these data have a multilevel structure, we will additionally assess caries incidence and prevalence using multilevel mixed effects Poisson and logistic modeling (ML-MEM). We will examine the effects of comprehensive prevention at multiple levels (tooth, child, grade, and school). In this analysis, we will be able to explore the variation in clinical outcomes across child and school levels. For all GEE and multilevel models, we will conduct analysis for outcomes (caries prevalence and incidence) measured by all teeth, all adult teeth only, and all deciduous teeth only.

5.4 Randomization and Blinding

Randomization. We will do a block randomization, generating sets of unique numbers to assign the experimental condition. Thus, for the first 30 schools we will generate 15 sets, each set containing a 1 or a 2, representing treatment assignment, in random order. We will repeat this in year 2 for the second set of 30 schools.

Blinding. As a pragmatic trial, this is non-blinded for the participants. Neither schools, nor teachers, nor students, nor clinicians will be blinded. Clinicians will, however, work in teams that only provide either simple or complex prevention. The analysts will be blinded as to the care provided to students in a particular school.

5.5 Compliance Assessment

This intervention trial depends on protocol compliance by clinicians, not students. We will train and calibrate clinicians during the summer before beginning each school year. To assess compliance we will use qualitative and quantitative methods together with audit and feedback.

Qualitatively, to ensure that the electronic records reflect actual implementation, we will visit each team in the fall and spring of each year for a one-day site visit. During the day, we will monitor adherence to protocol, particularly: student flow, caries diagnosis, and procedures delivered.

Quantitatively, we will use the elementary methods of statistical process control[71,72]. We will examine four domains: 1) informed consent rates; 2) caries prevalence (e.g.: diagnosis); 3) care provision; and 4) outcomes. We will monitor these domains using electronic records and then verify with in-person site visits. We will start with national averages and standard deviations for school-based informed consent rate (35%), untreated caries prevalence of (21.5%). All children (100%) with permanent bicuspids and molars should receive either silver diamine fluoride (simple prevention) or traditional sealants (complex prevention) and fluoride varnish. All children (100%) with caries on their posterior teeth should receive either silver diamine fluoride (simple prevention) or therapeutic sealants (complex prevention).

We will create histograms, Pareto charts, and control charts, at the school, grade, and clinician level to identify common cause and special cause variation. Control limits will be adjusted yearly based on prior year data. If a clinician, school or grade exhibits variation that is out of the control range we will use this audit to work with the clinical team and school to provide feedback. We will then create a fishbone diagram to identify the potential problem and attempt to rectify it. We will continue this process during the school year.

5.6 Prior and Concomitant Therapy

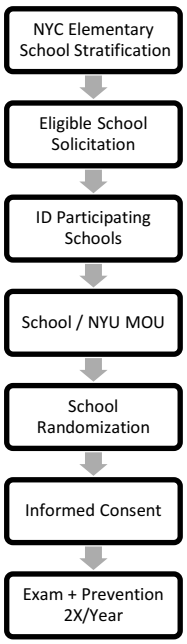
Not applicable

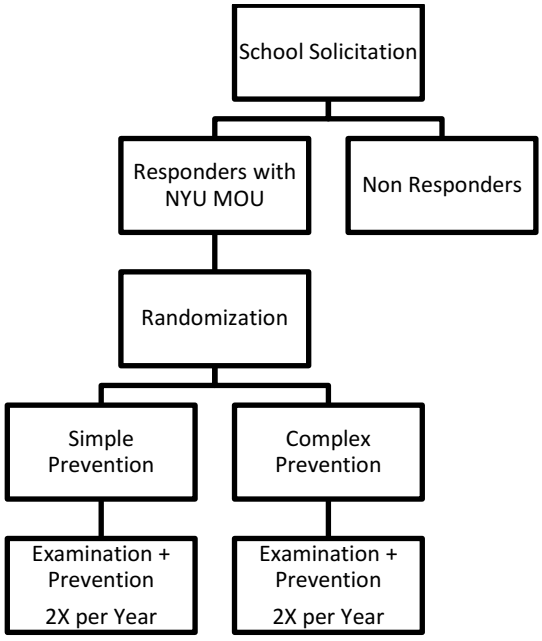
5.7 Receiving, Storage, Dispensing and Disposal

The products used for this trial are typical dental commodities obtained from Henry Schien. They include toothbrushes, toothpaste, fluoride varnish, silver diamine fluoride, and glass ionomer. They are shipped to New York University College of Dentistry and stored in a locked closet until used on the 8th floor with other clinical supplies.

6 Study Procedures

6.1 Study Procedures Table





Following stratification and solicitation, execution of MOU with individual schools, and randomization, care will be provided twice yearly in each participating schools. In year 1 care will be offered in 30 schools, and in year 2 an additional 30 schools.

7 Statistical Plan

7.1 Sample Size Determination

The study is powered to the primary outcomes of caries arrest and caries prevention. We expect to enroll approximately 14,100 students across 60 schools over the duration of the study (N=235 per cluster). From our pilot studies of school-based caries prevention, baseline caries prevalence is approximately 40%. Our power estimates assume an equal proportion of success, π, of 20% caries arrest. With a given non-inferiority margin (δ) of 10%, a total sample size per group of 198 (N_{tot} = 396) is required for an alpha of 5% and a power of 80% [73] . However, as we use a cluster randomized design, this sample size is inflated to account for clustering (intraclass correlation coefficient = .10) by a design effect of 24.4 to a total required sample of 9,662.

For caries prevention, both interim therapeutic restorations and silver diamine fluoride have been shown to be 80% efficacious in individual clinical trials[5,6]. Power for the repeated measures design was estimated using the method of Diggle et al (2002) for generalized estimating equations [74]. For power estimates, we control for the baseline prevalence of untreated decay. We assume a conservative average number of visits per child of 6, with a power of .80 and an alpha of 5%. We further assume a repeated measures correlation of 0.5 and a per-visit attrition rate of 20%. For a given minimally detectable effect size (standardized effect size difference) of .25, an attrition and clustering adjusted sample size of 12,874 is required. Thus, our study is powered for these conservative assumptions for caries prevention. Further, we note that in the presence of the nonlinear link function, ME-GLM is more powerful than GEE, thus our power estimates are conservative and the anticipated sample size is sufficient for analysis.

7.2 Statistical Methods

For the non-inferiority of simple prevention in caries arrest, we will first determine the per-patient proportion of carious lesions treated with simple versus complex prevention that stayed arrested throughout the length of the study. Each carious tooth treated with either simple or comprehensive prevention is a trial with outcomes either of caries arrest (1) or failure to arrest (0). The percentage of arrested caries (at the child level) will thus be modeled using multilevel binomial regression. Our noninferiority margin, δ, is set at 10%. Our null hypothesis is thus that the experimental treatment (simple prevention) is inferior to the standard treatment (complex prevention) by at least δ: $\pi_{simple} - \pi_{complex} \geq \delta$. Our alternative hypothesis is that $\pi_{simple} - \pi_{complex} < \delta$. We will use differences in effect sizes as estimated by confidence intervals to determine clinical non-inferiority of the two prevention methods.

For the prevention of new caries, we will use generalized estimating equations (GEE) with a logit link (caries prevalence) and a negative binomial link (caries incidence), assuming an exchangeable correlation matrix, to evaluate longitudinal effects of comprehensive care untreated decay. We will identify the number of teeth at risk for each child during each follow-up interval and determine the number of those teeth in which new caries is observed at the examination that ends that interval. Primary teeth lost in each interval and new permanent teeth will not contribute to data for that interval.

To explore non-linear trends in untreated decay between simple and complex prevention, we will use generalized additive models (GAMs) with non-parametric smoothers.

Longitudinal effects of simple and complex prevention on academic outcomes, compared to untreated children, will be analyzed using propensity score-matching and multilevel modeling. First, we will estimate propensity scores for each participant at baseline, establishing the probability of treatment assignment conditional on observed covariates (e.g., prior academic performance). Propensity scores will be used to match treatment students to students not receiving treatment, considering multiple forms of matching such as nearest neighbor and caliper. Treated students and matched comparators will then be analyzed using multilevel mixed effects linear regression (for academic achievement) and Poisson regression (for school absences).

7.3 Subject Population for Analysis

For caries arrest, participants will be analyzed using intent to treat (all randomized). All participants will be analyzed as randomized in the original randomization, regardless of whether or not they received an intervention. For caries prevention, quality of life, and academic outcomes, we will use all-treated. Any participant randomized to the study that received at least one treatment of an intervention.

7.4 Interim Analysis

There are no interim analyses in this study.

8 Safety and Adverse Events

8.1 Risks and Discomforts

All children will receive primary and secondary prevention. All preventive interventions are currently used in clinical practice. Therefore, potential risks for the children receiving preventive care are minimal, and identical to children obtaining care in a dental office. In this context, the greatest risk is an allergic reaction to fluoride varnish, silver diamine fluoride, or glass ionomer. As indicated previously, there are only two case reports of an allergic reaction to fluoride varnish, and none with the current carrier.

Silver diamine fluoride will change the color of carious lesions from dark brown to black. Our survey of parents in private practice and NYU College of Dentistry found that the majority of parents found staining acceptable on the posterior teeth, especially when the alternative was anesthetics with drilling and subsequent fillings (Crystal et al. Parental perceptions and acceptance of silver diamine fluoride staining. JADA, 2017. In press). In our survey of principals, nurses, teachers, and parents in our 2 NYC pilot schools, all were more concerned with lack of care access than color change.

To guard against untoward consequences of unexpected adverse events, all clinical staff are trained in CPR, and the school nurse is notified on our arrival and departure from schools.

8.2 Adverse Event Definitions

Adverse Event

An AE is any untoward or unfavorable medical occurrence associated with the participant's involvement in the research, whether or not considered related to the study intervention.

Serious Adverse Event

A SAE is an AE that meets any of the following criteria:

- Fatal or life-threatening
- Requires or prolongs inpatient hospitalization*
- Results in persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Is a significant and impacting event, which may not be immediately life threatening but is clearly of major significance. It may jeopardize the participant and may require intervention to prevent one of the other outcomes listed above.

AE that do not meet any of the criteria above should be regarded as ***non-serious***.

Unexpected Adverse Event

An AE is considered "unexpected" if it is not listed in the or at the specificity/severity that has been previously observed and/or specified in the investigational protocol or materials related to the study.

Adverse Event Reporting Period

The study period during which AEs must be reported is normally defined as the period from the initiation of any study procedures to the end of the study intervention follow-up.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study.

Post-Study Adverse Event

The investigator should follow all AEs until the events are resolved, the participant is lost to follow-up, or the event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant or his/her physician (if applicable) believes might reasonably be related to participation in this study.

Any AE occurring after the study period or after the participant has discontinued or terminated study participation that may reasonably be related to the study (e.g. death, cancer, a subsequently conceived offspring with a congenital anomaly) should be recorded and reported immediately.

8.3 Recording of Adverse Events

All adverse events occurring during the study period will be recorded. At each contact with the participant, the investigator will seek information on adverse events by specific questioning and examination. Information on all adverse events will be recorded on the electronic dental record and any appropriate CRFs immediately. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that participation in the study is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed to determine the final outcome.

8.4 Reporting of Serious Adverse Events and Unanticipated Problems

The investigator will conform to the AE reporting timelines, formats and requirements of NYUMC and any other applicable entities to which they are responsible. At a minimum, events that must be reported are those that meet one of the following (Refer to Sections 8.1 and 8.2):

- Related to study participation
- Unexpected
- Serious or involve risks to participants or others

For Narrative Reports of Safety Events
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report will include:

- Study identifier
- Study center
- Participant number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.4.1 Investigator Reporting: Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to participants or others. The following describes the NYUMC IRB reporting requirements:

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- **Unanticipated problems, including adverse events that are unexpected and related:**
  - Unexpected**:** An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
  - Related to the research procedures**:** An event is related to the research procedures if in the opinion of the principal investigator or sponsor; the event was more likely than not to be caused by the research procedures.
  - Harmful: either caused harm to participants or others, or placed them at increased risk

Other reportable events:
The following events also require prompt reporting to the IRB, though **no later than 5 working days**:

- **Complaint of a research participant** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- **Protocol deviations or violations** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - One or more participants were placed at increased risk of harm
  - The event has the potential to occur again
  - The deviation was necessary to protect a participant from immediate harm
- **Breach of confidentiality**
- **Incarceration of a participant** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the participant to remain on the study.

- **New Information indicating a change to the risks or potential benefits** of the research, in terms of severity or frequency (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; other research finds arm of study has no therapeutic value).

Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report, including a description of the event with information regarding the criteria above, a follow-up/resolution plan, and the need for revision of any applicable documents. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator's study file.

8.5 Unblinding Procedures

Not applicable. The clinician will be aware of the care provided.

8.6 Stopping Rules

Given that we are implementing preventive interventions used in clinical practice, and with the exception.

8.7 Monitoring of Events

It is the responsibility of the investigator to oversee the safety of the study at his/her site(s). Safety monitoring should include regular and 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 (Refer to Section 9).

8.7.1 Data Monitoring Committee

We will convene a data monitoring board, if required by PCORI.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study participants 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 participant of the following:

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

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of authorization. For participants 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 participant is alive) at the end of their scheduled follow-up period.

9.2 Source Documents

Source data is all information, original records of 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. For this trial the source documents include: informed consent, health history, examination and clinical care records. These are all collected electronically and maintained on a secure data base at the data coordinating center.

9.3 Case Report Forms

All study forms are electronic and reside on iPads. Forms require completion prior to moving to next steps. Out of range entries are flagged immediately for correction, if necessary, and re-entry.

9.4 Records Retention and Storage

All records are securely stored electronically on the data coordinating center servers. They will be stored for the term of the study.

9.5 Study/Regulatory Binder

We will create a study/regulatory binder per http://med.nyu.edu/regbinder/

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

N/A

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the funding sponsor, and University compliance and quality assurance groups of all study related documents. The investigator will also ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study will be conducted in compliance with the protocol approved by the IRB, GCP guidelines, and applicable NYUMC and federal regulatory requirements. No deviation from the protocol will be implemented without the prior review and approval of the IRB, except where it may be necessary to eliminate an immediate risk to a participant. In such case, the deviation will be reported to the IRB according to its policies and procedures.

This protocol and any amendments will be submitted to an IRB in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All participants will be provided a consent form describing the study and providing sufficient information for them to make an informed decision about their participation.

11.1 Funding Source

This study is financed through a grant from the Patient Centered Outcomes Research Institute

11.2 Conflict of Interest

None.

11.3 Participant Stipends or Payments

None.

12 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the PI or primary responsible party. Any

investigators involved with this study will be obligated to provide the PI or primary responsible party with complete test results and all data derived from the study.

13 Attachments

1. New York University / New York City MOU
2. Current New York City IRB approved Informed Consent

14 References

1. Marcenes W, Kassebaum NJ, Bernabé E, et al. Global burden of oral conditions in 1990-2010: a systematic analysis. *Journal of dental research.* 2013;92(7):592-597.
2. Dye B, Li X, Thornton-Evans G. Oral health disparities as determined by selected Healthy People 2020 Oral Health objectives for the United States, 2009-2010. *NCHS Data Brief.* 2012;104:1-8.
3. Dye BA, Thornton-Evans G, Li X, Iafolla TJ. Dental caries and sealant prevalence in children and adolescents in the United States, 2011-2012. *NCHS data brief.* 2015(191):1-8.
4. Griffin SO, Wei L, Gooch BF, Weno K, Espinoza L. Vital Signs: Dental Sealant Use and Untreated Tooth Decay Among U.S. School-Aged Children. *MMWR Morbidity and Mortality Weekly Report ePub: 18 October 2016.* 2016.
5. Pine CM, Harris RV, Burnside G, Merrett MC. An investigation of the relationship between untreated decayed teeth and dental sepsis in 5-year-old children. *British dental journal.* 2006;200(1):45-47; discussion 29.
6. Otto M. For want of a dentist. *The Washington Post.* February 28, 2007, 2007.
7. Hosseinipour N, Jasek J, Summers C. Oral Health in New York City. *NYC Vital Signs* 2012;11(5):1-4.
8. Cruz GD, Chen Y, Salazar CR, Karloopia R, LeGeros RZ. Determinants of oral health care utilization among diverse groups of immigrants in New York City. *Journal of the American Dental Association.* 2010;141(7):871-878.
9. Cruz GD, Chen Y, Salazar CR, Le Geros RZ. The association of immigration and acculturation attributes with oral health among immigrants in New York City. *Am J Public Health.* 2009;99 Suppl 2:S474-480.
10. Webster AE, Johnson CN, Philadelphia PA. *Preparation of cavities for fillings.* 1909.
11. Downer MC, Azli NA, Bedi R, Moles DR, Setchell DJ. How long do routine dental restorations last? A systematic review. *British dental journal.* 1999;187(8):432-439.
12. Chadwick B, Treasure E, Dummer P, et al. Challenges with studies investigating longevity of dental restorations--a critique of a systematic review. *Journal of dentistry.* 2001;29(3):155-161.
13. Burke FJT, Lucarotti PSK. How long do direct restorations placed within the general dental services in England and Wales survive? *British dental journal.* 2009;206(1):E2; discussion 26-27.
14. HHS. *Promoting and Enhancing the Oral Health of the Public.* http://www.hrsa.gov/publichealth/clinical/oralhealth/hhsinitiative.pdf2010.
15. CMS. Improving Access to and Utilization of Oral Health Services for Children in Medicaid and CHIP Programs. 2011.
16. ADA. Breaking Down Barriers to Oral Health for All Americans: The Role of the Workforce. Chicago IL: American Dental Association; 2011.
17. ADA. Action for Dental Health: Bringing disease prevention into communities. 2013.
18. Isman B. First 5: Oral Health Resource Guide. Sacramento: First 5 California; 2014: http://first5oralhealth.org/rural_smiles/downloads/chapter1/Potential%20Barriers.pdf. Accessed July 2015.
19. Vujicic M. Time to rethink dental "insurance". *Journal of the American Dental Association.* 2016;147(11):907-910.
20. Niederman R, Feres M, Ogunbodede E. Dentistry. In: Debas HT, Donkor P, Gawande A, Jamison DT, Kruk ME, Mock CN, eds. *Disease Control Priorities Essential Surgery.* Vol 1. Washington DC: World Bank Group; 2015:173-195.

21. Niederman R, Gould E, Soncini J, Tavares M, Osborn V, Goodson JM. A model for extending the reach of the traditional dental practice: the ForsythKids program. *Journal of the American Dental Association (1939).* 2008;139(8):1040-1050.
22. Ruff RR, Palmisano J, Niederman R. Assessing Clinical Effectiveness of Rural Colorado School-Based Caries Prevention Programs. *BMC Oral Health.* 2017;(Submitted).
23. Parnell C, Whelton H, O'Mullane D. Water fluoridation. *European archives of paediatric dentistry : official journal of the European Academy of Paediatric Dentistry.* 2009;10(3):141-148.
24. McDonagh MS, Whiting PF, Wilson PM, et al. Systematic review of water fluoridation. *BMJ (Clinical research ed).* 2000;321(7265):855-859.
25. Griffin SO, Regnier E, Griffin PM, Huntley V. Effectiveness of fluoride in preventing caries in adults. *Journal of dental research.* 2007;86(5):410-415.
26. Johnson N, Lalloo R, Kroon J, Fernando S, Tut O. Effectiveness of water fluoridation in caries reduction in a remote Indigenous community in Far North Queensland. *Australian dental journal.* 2014.
27. Wong MCM, Clarkson J, Glenny AM, et al. Cochrane reviews on the benefits/risks of fluoride toothpastes. *Journal of dental research.* 2011;90(5):573-579.
28. Dos Santos AP, Nadanovsky P, de Oliveira BH. A systematic review and meta-analysis of the effects of fluoride toothpastes on the prevention of dental caries in the primary dentition of preschool children. *Community Dent Oral Epidemiol.* 2012.
29. Marinho VCC, Worthington HV, Walsh T, Clarkson JE. Fluoride varnishes for preventing dental caries in children and adolescents. *The Cochrane database of systematic reviews.* 2013;7:CD002279.
30. Mickenautsch S, Yengopal V. Caries-preventive effect of glass ionomer and resin-based fissure sealants on permanent teeth: An update of systematic review evidence. *BMC research notes.* 2011;4:22.
31. Yengopal V, Mickenautsch S, Bezerra AC, Leal SC. Caries-preventive effect of glass ionomer and resin-based fissure sealants on permanent teeth: a meta analysis. *Journal of oral science.* 2009;51(3):373-382.
32. Ahovuo-Saloranta A, Forss H, Walsh T, et al. Sealants for preventing dental decay in the permanent teeth. *The Cochrane database of systematic reviews.* 2013;3:CD001830.
33. Ricketts D, Lamont T, Innes NPT, Kidd E, Clarkson JE. Operative caries management in adults and children. *The Cochrane database of systematic reviews.* 2013;3:CD003808.
34. de Amorim RG, Leal SC, Frencken JE. Survival of atraumatic restorative treatment (ART) sealants and restorations: a meta-analysis. *Clinical oral investigations.* 2012;16(2):429-441.
35. Schwendicke F, Dörfer CE, Paris S. Incomplete caries removal: a systematic review and meta-analysis. *Journal of dental research.* 2013;92(4):306-314.
36. Rosenblatt A, Stamford TCM, Niederman R. Silver diamine fluoride: a caries "silver-fluoride bullet". *Journal of dental research.* 2009;88(2):116-125.
37. Zhi QH, Lo ECM, Lin HC. Randomized clinical trial on effectiveness of silver diamine fluoride and glass ionomer in arresting dentine caries in preschool children. *Journal of dentistry.* 2012;40(11):962-967.
38. Liu BY, Lo ECM, Chu CH, Lin HC. Randomized trial on fluorides and sealants for fissure caries prevention. *Journal of dental research.* 2012;91(8):753-758.
39. Mariño RJ, Khan AR, Morgan M. Systematic review of publications on economic evaluations of caries prevention programs. *Caries research.* 2013;47(4):265-272.
40. Källestål C, Norlund A, Söder B, et al. Economic evaluation of dental caries prevention: a systematic review. *Acta odontologica Scandinavica.* 2003;61(6):341-346.
41. Griffin SO, Naavaal S, Scherrer C, Patel M, Chattopadhyay S, Force CPST. Evaluation of School-Based Dental Sealant Programs: An Updated Community Guide Systematic Economic Review. *Am J Prev Med.* 2016.
42. Schwendicke F, Stolpe M, Meyer-Lueckel H, Paris S, Dörfer CE. Cost-effectiveness of one- and two-step incomplete and complete excavations. *Journal of dental research.* 2013;92(10):880-887.
43. Mickenautsch S, Yengopal V. Failure rate of high-viscosity GIC based ART compared with that of conventional amalgam restorations--evidence from an update of a systematic review. *SADJ : journal of the South African Dental Association = tydskrif van die Suid-Afrikaanse Tandheelkundige Vereniging.* 2012;67(7):329-331.

44. Mickenautsch S, Yengopal V, Banerjee A. Atraumatic restorative treatment versus amalgam restoration longevity: a systematic review. *Clinical oral investigations.* 2010;14(3):233-240.
45. Niederman R, Leitch J. "Know what" and "know how": knowledge creation in clinical practice. *Journal of dental research.* 2006;85(4):296-297.
46. Griffin SO, Barker LK, Wei L, et al. Use of dental care and effective preventive services in preventing tooth decay among U.S. Children and adolescents--Medical Expenditure Panel Survey, United States, 2003-2009 and National Health and Nutrition Examination Survey, United States, 2005-2010. *Morbidity and mortality weekly report Surveillance summaries.* 2014;63 Suppl 2:54-60.
47. USDHHS. Annual EPSDT Participation Report Form CMS-416, Fiscal year: 2013. Washington DC: U.S. Department of Health and Human Services, Centers for Medicaid and Medicare Services. ; 2014.
48. Tellez M, Gray SL, Gray S, Lim S, Ismail AI. *Sealants and dental caries: dentists' perspectives on evidence-based recommendations.* Sep 2011.
49. School-Based Oral Health Services: A Select Bibliography. Government/National Reports. 2012; http://www.healthinschools.org/Health-in-Schools/Health-Services/School-Based-Dental-Health/Dental-Health-Bibliography.aspx. Accessed November 26, 2014.
50. National Prevention Strategy. 2011; http://www.surgeongeneral.gov/initiatives/prevention/strategy/index.html.
51. Oral Health Goals. http://www.healthypeople.gov/2020/topics-objectives/topic/oral-health, 2015.
52. Educational & Community-Based Program Goals. 2010; http://www.healthypeople.gov/2020/topics-objectives/topic/educational-and-community-based-programs.
53. IOM. *Children and Adolescent Health and Health Care Quality: Measuring What Matters.* Washinton DC: The National Academies Press; 2011.
54. IOM. *Children and Adolescent Health and Health Care Quality: Measuring What Matters.* Washington DC: The National Academies Press; 2011.
55. CDHP. Dental Sealants: Proven to Prevent Tooth Decay. 2014.
56. NNOHA. *Survey of School-Based Oral Health Programs Operated by Health Centers.* Denver Colorado 2014 2014.
57. Niederman R, Huang SS, Trescher A-L, Listl S. Getting the incentives right: Improving oral health equity with universal school-based caries prevention. *American Journal of Public Health.* 2017 (in press).
58. Niederman R, Gould E, Soncini J, Tavares M, Osborn V, Goodson JM. A model for extending the reach of the traditional dental practice: the ForsythKids program. *Journal of the American Dental Association.* 2008;139(8):1040-1050.
59. Niederman R. Bringing Care to People Rather Than People to Care. *Am J Public Health.* 2015;105(9):1733.
60. Kohn LT, Corrigan J, Donaldson MS. *To err is human : building a safer health system.* Washington, D.C.: National Academy Press; 2000.
61. Niederman R. Bringing Care to People Rather Than People to Care. *Am J Public Health.* 2015:e1.
62. Arrow P, Klobas E. Minimal Intervention Dentistry for Early Childhood Caries and Child Dental Anxiety: A Randomised Control Trial. *Australian dental journal.* 2016.
63. Arrow P, Klobas E. Child oral health-related quality of life and early childhood caries: a non-inferiority randomized control trial. *Australian dental journal.* 2016;61(2):227-235.
64. U.S. C. Bronx County, NY. 2015; http://www.census.gov/search-results.html?q=bronx+ny&search.x=0&search.y=0&search=submit&page=1&stateGeo=none&searchtype=web, 2016.
65. NYC. NYC School Metrics. In: Education NDo, ed. New York, NY: New York City Department of Education; 2016.
66. De Stefano M. New York City, Department of Education. In: Niederman R, ed2014.
67. Beltran ED, Malvitz DM, Eklund SA. Validity of two methods for assessing oral health status of populations. *J Public Health Dent.* 1997;57(4):206-214.
68. White JA, Beltran ED, Malvitz DM, Perlman SP. Oral health status of special athletes in the San Francisco Bay Area. *Journal of the California Dental Association.* 1998;26(5):347-354.

69. Petersen PE, Baez RJ. *Oral Health Surveys: Basic Methods.* Geneva: World Health Organization; 2013.
70. Dye BA, Barker LK, Li X, Lewis BG, Beltran-Aguilar ED. Overview and quality assurance for the oral health component of the National Health and Nutrition Examination Survey (NHANES), 2005-08. *J Public Health Dent.* 2011;71(1):54-61.
71. Benneyan JC, Lloyd RC, Plsek PE. Statistical process control as a tool for research and healthcare improvement. *Qual Saf Health Care.* 2003;12(6):458-464.
72. Provost LP, Murray SK. *The Health Care Data Guide. Learning from data for improvement.* San Francisco: Jossey-Bass; 2011.
73. Chow S, Shao J, Wang H. *Sample size calculations in clinical research* Boca Raton, Florida: Taylor & Francis; 2008.
74. Diggle PJ, Heagerty P, Kung-Yee L, Zeger SL. *Analysis of Longitudinal Data.* Oxford U.K.: Oxford University Press; 2002.

General Design Flowchart