- Official Title: Effectiveness of Silver Diamine Fluoride in Arresting Early Approximal Carious Lesion Progression: A Pilot Study
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Objective: The objective of this study is to evaluate the effectiveness of 38% Silver Diammine Fluoride (SDF) in arresting initial non-cavitated approximal carious lesion in adults aged 21-64 years utilizing three methods: pairwise comparison of individual radiographs, visual assessment of subtraction radiographs and histogram analysis of subtraction radiographs.

Design: This study is a randomized, triple-blinded, and placebo-controlled clinical trial (*ClinicalTrials.gov identifier-NCT02591147***).** The study population consisted of adults aged 21-64 years old who are seeking care at the University of Iowa, College of Dentistry and Dental Clinics. Eligibility for the study includes having at least one initial non-cavitated approximal posterior carious lesion (Radiologic scores RA1, RA2, or RA3 using the International Caries Classification and Management System (ICCMS) scoring system) that was in contact with an adjacent non-restored tooth surface.

Methods: Consented subjects will be randomly assigned to one of the two study arms, either treatment (38% SDF solution) or placebo (water) designated as solutions "A" and "B". Participants will complete beverage intake and caries risk questionnaires at baseline and 12 months. The selected lesion will be followed at 6 and 12 months. A bitewing radiograph will be made at baseline utilizing a bite registration holder to insure close geometrical alignment of subsequent follow up radiographs. Lesion progression will be monitored radiographically through three methods: pairwise comparison of individual radiographs, visual assessment of subtraction radiographs and histogram analysis of subtraction radiographs.

Statistical Analysis Plan: The primary outcome of interest is whether there is caries progression based upon radiographic evaluation, evaluated at 12 months, for the two study arms. The analytic approach, which will utilize binary logistic regression modeling for correlated data, will consider the dependencies (correlations among data points) that typically arises with longitudinal data. For analyses targeting a specific time point, this is not a concern, because there is only a single measurement per individual, and standard binary logistic regression methods can be applied. A widely accepted method to deal with these types of dependencies is using generalized estimating equations (GEE). We will also consider mixed modeling approaches as part of these investigations as appropriate. Model selection will be guided by the use of Akaike's criterion and its modifications; particular considerations will be given to selection of the covariance structure addressing data dependencies, for which approaches have been developed in both the GEE and mixed modeling contexts. A primary goal in all analyses will be to formally compare the two treatment arms and, in doing so, to obtain estimates of effect sizes and associated variability for the planning of future trials. Throughout, the primary covariate of interest will be treatment arm; the effects of covariates including patient demographics, dietary intakes and behaviors, other aspects of caries risk assessment, and caries score (DMFT/DMFS) as a measure of disease burden and risk will also be assessed. All analyses will be carried out in accordance with intention-to-treat principles. The analyses just described will provide estimates of treatment effects and associated measures of variability to assist in planning a future definitive trial. In addition, attrition rates will be estimated, and 95% confidence intervals will be constructed for each time point and treatment arm. Because there is evidence that silver diamine fluoride is also a preventive agent, assessment of differences in incident caries between the two treatment groups is of particular interest as a secondary aim. We will consider measures reflecting the development of new lesions, considering issues of tooth eruption and loss between examinations (caries increment). The crude caries increment will be supplemented with net caries increment allowing for examiner reversals, and with the adjusted caries increment. Poisson models, or Poisson models augmented with an over dispersion parameter or an

extension to account for zero count inflation, have generally been found useful for examining the relationships between counts of affected teeth or surfaces, and can be applied to incident disease while accounting for correlated outcomes, including correlations among surfaces or subgroups of surfaces within an individual. Alternatives, such as the negative binomial model, are available if the Poisson is not appropriate. We note that linear regression approaches have sometimes been appropriately used to model caries increment. Candidate independent variables are as described above. Inter-and intra-rater reliability will be assessed for both radiographic and clinical measures of progression, using intraclass correlations for quantitative outcomes, and kappa statistics for categorical outcomes; weighted kappa will be used for ordinal categorical measures. Relationships between radiographic and clinical measures of progression will be assessed, using Spearman rank correlation when the two measures being compared are ordinal or quantitative. Binary outcomes (presence or absence of progression) will be assessed using McNemar's test (or the exact binomial test if appropriate); in this instance, evaluation of the level agreement of the two approaches will also be assessed using unweighted kappa. Descriptive statistics and graphics will further illustrate any identified relationships.