The Effectiveness of Silver Diamine Fluoride as a Treatment for Caries in Comparison to Traditional Restorative Techniques: A 12 Month Randomized Controlled Trial

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1. Introduction

Dental caries is the most common chronic disease in children, and is even four times as common as asthma in adolescents.[1] According to the National Health and Nutrition Examination Survey (NAHNES) from 1999 – 2004, 27.9 percent of children ages 2 – 5 have caries in the primary dentition, and that number increases to 51.17 for ages 6 – 11. When the income level for these children's families is 200 percent that of the Federal Poverty Level, 42 percent of children have caries, but when compared to those at 100 percent of the poverty level the caries rate reaches that of 54.3 percent of children, with 32.3 percent of children at this level of poverty having untreated decay.[2] For these children, living with this untreated dental disease may lead to problems with food intake, daily sleep, difficulty in school, restriction of daily activities, and negative impact to their self-esteem.[3] Primary prevention of caries in children is always preferable, but is not always possible. When primary prevention fails, effective secondary prevention using treatments that are safe, simple, low-cost, and acceptable to patients can be efficacious in preventing morbidity to these children, which is our ultimate goal.[4]

2. Objectives

The objectives of this clinical study are to evaluate:

- The effectiveness of treatment of cavitated caries in children by application of silver diamine fluoride (SDF) in comparison to conventional restorative treatments
- The perceptions of parents and patients to both treatment modalities and their levels of acceptability
- The opinions of dental providers in terms of ease of use and clinical time spent
- The relative cost-effectiveness of the two treatment approaches regarding both practitioner chair time and material-based cost

3. Review of Literature

3.1. Silver in Dentistry

Silver has been used in medicine for hundreds, even thousands, of years.[5] Some of the earliest reports of the use of silver compounds in dentistry to reduce the incidence of caries in the primary dentition date back to the 1840s.[6] In the late 60's and early 70's research by many groups worldwide began regarding the use of silver diamine fluoride to prevent caries.[7,8,9,10] In more recent years, clinicians have come to the realization that finding treatments especially for those children in disadvantaged communities, is of utmost importance on a worldwide level. Because of the great need and often the inaccessibility of standard dental care, discussions have arisen regarding Arresting Caries Treatment (ACT) as opposed to traditional restorative dental treatments, which typically would involve complete caries removal and replacement of missing tooth structure with a restoration.[11] Silver diamine fluoride offers many proposed advantages as an ACT – 1. It offers control of pain and infection. 2. Its ease of use is great. 3. It is highly affordable. 4. There is minimal time involvement for its application. 5. It is a non-invasive option.[12]

3.2. Silver Diamine Fluoride Mechanism of Action

The favored caries prevention agent today worldwide is fluoride, and professional topical fluoride applications, such as fluoride varnish are now-a-days the most commonly used strategy in the U.S. for primary and secondary prevention of carious lesions, even though this caries prevention use for varnishes is off-label in the U.S. This use has been endorsed by organized dentistry in the U.S., including the American Dental Association, the American Academy of Pediatric Dentistry, State preventive programs funded by the Centers for Disease Control and Prevention, etc. SDF is a type of professional topical fluoride which has been approved in the U.S. with an application similar to that of fluoride varnishes.[13] In fact, Oregon now allows hygienists and expanded function dental assistants to apply SDF under general supervision just as with any other fluoride or antimicrobial agent.[14] SDF incorporates both of the advantages of fluoride to reduce dental caries and promote remineralization, and also offers a quite potent germicidal effect.[12] It has been reported that it not only strengthens the sound tooth structure, but also offers the ability to kill bacteria and arrest caries progression once a cavity has developed.[12] Research has shown that SDF has the ability to

inhibit colonization of *Streptococcus mutans*, *Actinomyces naeslundii*, and *Enterococcus faeclis*.[4] Being of utmost importance to the caries progression process, the direct effects on *S. mutans* have been noted for years, with literature dating back to 1976.[15] It is important to note that not only does SDF have the ability to prevent biofilm formation, but it also has the ability to kill the bacteria present at time of placement.[16]

In addition to directly inhibiting bacterial growth, SDF also can reduce against acid solubility and facilitate enamel remineralization via other mechanisms.[4] Early researchers believed the silver-salt formation stimulated sclerotic or calcified dentin formation.[12] For decades now, it continues to be shown that the fluoride and silver present in SDF interact together to form fluorapatite strengthening the tooth.[8] It has also been shown that not only is the depth of penetration of SDF far greater than that of other fluoride containing materials, but the tooth retains two to three times more SDF than with other fluoride combinations.[17] Furthermore, the amount of reparative dentin formation has shown great increase when used prior to dental materials that have silver added.[18] The combination of all this information demonstrates why SDF has been shown to be such an effective desensitizer as well.[19] In comparison to active carious lesions with no treatment, those which were arrested at 24 months via biannual SDF application showed more well aligned and highly organized crystallites.[20] The underlying collagen fibers were protected from exposure, and there was also a rich zone of calcium and phosphate, suggesting that clinically there is a highly positive effect on dentin remineralization due to the SDF application.[20]

3.3. Previous Research Involving Silver Diamine Fluoride

Research over the past few decades regarding the effectiveness of SDF has been relatively consistent. In comparison to 5 percent sodium fluoride (NaF; used commonly in professionally applied fluoride varnishes), 38 percent SDF was found to be more effective in arresting active caries in the primary anterior teeth of preschool children at 30 month follow-up.[21] Continued research showed that not only could SDF arrest active caries, but additionally it could reduce the incidence of caries in the primary teeth as well as the first permanent molars in school children.[22] Most recently it has been shown that annual SDF application has a similar rate of effectiveness in

arresting caries comparable to that of sealant placement or biannual application of 5 percent NaF after 24 months.[23]

3.4. Negative Aspects of Silver Diamine Fluoride

In addition to the numerous apparent positive effects of SDF there are a minimal number of drawbacks, the most notable being the black stain it leaves on the carious dentin.[12] While esthetically unpleasing to some, this black stain is not of any physical harm to the patient. [19, 21] In fact when compared to applications of sodium fluoride and no treatment, all treatments had teeth presenting at recall with blackened dentin.[21] Recent studies have shown this black discoloration appears to be a non-issue, as the coloration of the teeth following treatment did not decrease patient satisfaction.[21] However, additional research has still been aimed at reducing the black discoloration of the tooth by placing potassium iodide (KI) following SDF application or by completely placing an alternative agent, such as ammonium hexofluorosilicate ($(NH_4)_2SiF_6$).[4] Placing potassium iodide may eliminate the staining, but whether this reduces the effectiveness of the SDF is still in need of further evaluation, especially in vivo.[24] Research on ammonium hexofluorosilicate, on the other hand, shows that it is not effective in reducing caries progression and is therefore not a viable replacement option to SDF.[4]

The most common concern with any product used intraorally is its compatibility with intraoral soft-tissues. Recent research has confirmed that tissue ulcerations and argyria were not present following treatment with SDF.[19] Only transient mild erythema of the gingiva near the SDF-treated tooth and a metallic taste in the patients' mouths were noted in some patients, supporting that the use of silver diamine fluoride is quite safe. [19, 21]

3.5. Silver Diamine Fluoride Variations in Application

While much of the previously presented research suggests that there are potential positive effects of SDF, there are still many potential variations in regimens for application. Many would assume that for effective arrest of caries, it would be important for carious debris to be removed reducing the bacterial load.[25,26] However, it has been shown that caries removal did not offer any significant beneficial effect in terms of arresting carious lesions and only showed a reduction in the number

of arrested lesions that turned black in the NaF group, as 100 percent of the lesions in the SDF group presented with a black coloration regardless of caries removal.[21] For this reason, it has been suggested that caries removal would be unnecessary, which would make the procedure more simple and could increase the potential for patient acceptability which is important because it is one of the advantages of this product.[21]

Many studies have shown a variation in number of applications and concentrations, leading to the research question of determining an exact regimen.[4] In terms of concentration, when observed at 6 months, it was noted that a single application of 38 percent SDF could arrest caries in comparison to 12 percent SDF, which could not.[27] Regarding the optimal number of applications, it was shown that an annual topical application of 38 percent SDF would arrest 37 percent of caries at 12 months and up to 79.2 percent of caries at 24 months, while biannual applications resulted in 53 percent arrested caries at 12 months and 90.7 percent arrested caries at 24 months.[28]

Due to the potentially highly positive caries arrest effects of SDF, research has been conducted in an attempt to prevent washing away of the product when placed on the tooth surface.[29] It has been postulated that if the treated surface was to turn instantaneously black, this would indicate that the process had been accelerated and was in turn more effective.[29] Studies have shown that applications of 10% stannous fluoride or tannic acid were not shown to have an additional benefit in arresting caries although they may have appeared to accelerate the process of SDF uptake by the tooth surface.[29,27]

3.6. Current Research

According to Rosenblatt at el., the advantages of SDF are numerous. While it can control the infection, it is also easy to use, highly affordable, involves minimal chair time, and is quite non-invasive.[12] They also concluded there is no [published] research that addresses all of these topics. SDF was approved in the United States in July 2014 and currently there have been no clinical trials in the United States testing the application of SDF to arrest caries in children. [13] Also, there seem to be no studies that address the failure rates of SDF in comparison to conventional one and two-surface restorations for the treatment of dentin caries. The researchers' aims in this study will be

to address affordability, ease of use, and both patient/parent and provider acceptance, in addition to clinical success rates when compared to conventional restorations.

4. Materials and Methods

4.1. Purpose

To determine the effectiveness of the application of silver diamine fluoride (SDF) in comparison to conventional restorative treatments in International Caries Detection and Assessment System criteria (ICDAS) 5 and 6, one and two surface carious lesions in primary molars which will be assessed based on major and minor failure criteria when followed for one year. Additionally, parents'/children's and providers' perceptions will be assessed as well as the cost of both regimens, to include both chair time spent and materials' costs.

4.2. General Outline

Children, 2-10 years of age will be invited to participate. The original study site is Mott Children's Health Center (MCHC) in Genesee County, Michigan. Following a slow recruitment period, the University of Michigan School of Dentistry (UMSOD) Children's Clinic was added as a second study site. Given the current data in the literature, the combined failure rate for conventional restorative techniques (e.g. compomers) is approximately 29% at one year follow-up,[30] while application of silver diamine fluoride has a failure rate of 63% at one year follow-up, with increased success over time.[28] Although the failure rate of SDF at one-year follow-up seems alarming, as indicated by Zhi, *et al.* it may be possible to increase the success rate with additional applications providing success rates up to 90.1% at 24 months. [28] Using these data, α-value of 0.05 and a Power set at 80%, the resulting sample size would be 68 (34 per group) as calculated using the software, nQuery (Appendix 1). To account for 30% attrition, the final number needed for the initial study will be 98 (92 for 25% attrition, 86 for 20% attrition). Subjects will be contacted by phone regularly and invited to two intermediate clinic visits (plus a final study visit) to reduce attrition (Table 1). Given a review of the current literature of the few Randomized Controlled Clinical Trials involving SDF worldwide, the majority of this research has been completed with pre-school aged children. Almost all research discusses arresting or prevention of caries in the

primary dentition, as well as prevention of caries on first permanent molars. Due to the strength of the current research, this study will be focused on the primary dentition of children in the U.S. These children and their parents will be approached when presenting for examination/recall/or treatment at Mott Children's Health Center, Flint, MI, or the University of Michigan School of Dentistry Children's Clinic, Ann Arbor, MI. Interested families with children that qualify following screening examination will be provided with an *Informed Consent*/*Assent* (Appendix 3) and an *Enrollment Information Form* (Appendix 4).

4.3. Inclusion and Exclusion Criteria

Eligible children will be identified during a screening at initial presentation. They must fulfill the inclusion criteria which include (Appendix 10, CRF 10):

- Patients must be ages 2-10.
- Presence of at least one active (soft) cavitated carious lesions in the primary dentition, extending into dentin (ICDAS 5 or 6) – Only one tooth will be selected for the study. All others will be restored and monitored according to the American Academy of Pediatric Dentistry (AAPD) guidelines.
- The selected tooth must have a one or two surface lesion (more than 1/3 of the crown of the tooth must be remaining) and must allow for direct application of SDF.
- Study teeth will not have any spontaneous or elicited pain due to caries, tooth mobility, or signs of pulpal infection.
- Selected primary teeth must have an anticipated exfoliation date greater than 12 months away.

Exclusion criteria include children with:

- Hereditary developmental defects such as Amelogenesis Imperfecta and Dentinogenesis Imperfecta
- Severe medical conditions that do not allow the child to be managed in the MCHC/UMSOD clinics
- Known allergy /sensitivity to dental materials being used, including SDF

- Inability of the child to cooperate for treatment, recall examinations, or periapical radiographs.
- Wards of the State, for consenting reasons

After approaching the parent with a brief discussion of the study, determining interest and asking brief pre-screening eligibility questions as approved by the Institutional Review Board (IRB), the informed consent process will occur. Parents will provide both written and verbal consent, and written and verbal assent will also be asked of the children older than age 8 (Appendices 2 &3). Following the informed consent process, full study eligibility criteria will be reviewed with the pediatric dental resident performing the procedure. At time of consent, the parent will also be provided the *Enrollment Information Form* (Appendix 4) as a reminder of important information and frequently asked questions. This form will include information regarding study purpose, duration (12 months, including application/restorative appointment, 3 follow-up visits, and additional follow-up phone calls/contacts), possible resulting appearance, and overall study protocol.

Children who are enrolled to participate in the study will receive a full mouth caries examination using the ICDAS criteria (Examiners will be trained and calibrated in the ICDAS criteria prior to study initiation.), and will be randomly divided into two groups:

1. **Conventional management of caries group**: This group will receive traditional restorative care for one tooth with a one or two surface lesion – including composite, amalgam, or glass-ionomer restorations according to the current AAPD treatment guidelines.

2. **SDF management of caries group**: This group will receive applications of SDF applied to their carious lesion, in lieu of restoration placement, with the goal of "arresting caries".

4.4. Participant Allocation and Blinding

Subjects enrolled in the study will be randomly assigned to one of the two caries management groups in a 1:1 ratio. Although treatment will be randomly assigned, it will not be possible to blind parents, children, or dentists to the assigned treatment group as the post-operative appearance is likely to differ markedly between groups. In the event treatment for the patient is failing, regardless of the treatment arm assigned, the provider will recommend additional treatment and can withdraw the patient at any time and appropriate reasoning will be recorded. Patients/parents have the right to withdraw from the study at any time and for any reason as well. Additionally their reasoning for withdrawal will be recorded (Appendix 10, CRF 04, 11, 14-17).

5. Interventions

Patients will be randomly assigned to the following groups, and managed under that philosophy for a 12 month period. Each appointment for either intervention group will follow the designated *Workflow* for that appointment (Appendix 5-8) and appropriate subsequent documents will be completed at each visit (Appendix 9).

5.1. Conventional management of caries

These children will receive restorative dental care in alignment with the AAPD guidelines, within the confines of the MCHC or UMSOD clinics. This treatment typically includes administration of local anesthesia, placement of rubber dam, caries removal with rotary and hand instruments, and placement of a final restoration. Following completion of the conventional caries management, the provider will complete the *CRF 02 Intervention Visit: Conventional Restoration* CRF (Appendix 10, CRF 02). For both study interventions, fluoride varnish application should not be applied within one week before or after study intervention so that the effects noted will not be confused with known positive effects of topical fluoride varnish applications.

5.2. SDF management of caries

- The selected tooth with notable decay into dentin will be isolated with cotton rolls.
- No caries removal will be performed, except for food or other obvious debris.[21]
- Tooth will be dried with gauze and SDF solution will be placed on the carious dentin until it is saturated.
- Excess SDF will be blotted dry with a cotton pellet.
- A second application of SDF solution will then be placed to ensure that the entire carious surface is wetted, and excess will again be blotted with a cotton pellet.
- Following the second application of SDF, the area will be isolated for 3 minutes to allow for ample drying before allowing contact with saliva and soft tissues
- Should the SDF come in contact with any soft tissues, soft tissue should immediately be wiped with a saline wipe
- Following completion of the SDF intervention visit, the provider will complete the CRF 03 *Intervention Visit: Silver Diamine Fluoride* CRF (Appendix 10, CRF 03).
- A second application of SDF will be applied at 6 month recall, following the same protocol as noted above (Due to the potential for increased caries arrest rate with a 6 month application[28]).
- Any new carious lesions that develop after the initial treatment will be recorded, and treated using conventional treatment methods and will not be included in the study.
- Following the completion of this study, teeth in the SDF group will be treated according to AAPD guidelines or observed for exfoliation. The parent of an SDF treated child can elect a restoration following AAPD guidelines at the 12 month visit.

Both groups will receive the following, according the standard procedures at the MCHC/UMSOD:

- Oral Health Instruction (OHI) and diet instruction
- Tooth brushing/dentifrice use at home
- Fissure sealants for permanent teeth will be placed if deemed necessary.
- Traditional preventative care at recalls based on AAPD guidelines (Regular recall exams, prophylaxis, scaling, flossing, and fluoride varnish at 6 month recalls will be provided for both treatment arms. Special care will be taken to not apply fluoride varnish directly to the carious lesion which is being treated with SDF.)

6. Study Visits and Intermediate Contacts

Recalls for both groups will occur via phone questionnaire as well as follow-up visits. Participants will be contacted at 1 month, 2 months, 4.5 months and 9 months (± 2 weeks) following restoration placement or application of SDF. Subjects will need to present to the clinic for follow-up visits at 3 months (± 6 weeks), 6 months (± 6 weeks), and for study completion at 12 months (± 6 weeks) (Table 1). Subjects will also be called to schedule and confirm these follow-up visits; these short calls will require no payment to the study subjects. In the case of an emergency, an emergency visit will be scheduled at Mott Children's Health Center or the University of Michigan School of Dentistry. An emergency will be evaluated and treated according to the AAPD guidelines, followed by completion of appropriate case report forms (CRFs) and reporting to IRBs and study sponsors (Appendix 10, CRF 14-17). In the event of minor or major failure in either study group, the subject will we withdrawn from the study and teeth will be given the appropriate treatment as stated in the AAPD Guidelines free of charge, these teeth will be categorized as a failure, and a *CRF 04 Treatment Deviation CRF (Appendix 10, CRF 04)* will be completed.

Table 1. Patient Contact Interval

Patient Contact	Recall Interaction	Time Scale
Clinic Visit #1	Consent/Assent, baseline questionnaires, initial caries assessment, radiographs*, intervention	T = 0
Intermediate Contact	Attrition prevention, update contact information, follow-up on pain	T = 1 month, 2 months (Additional reminder for Clinical Visit #2)
Clinic Visit #2	Assessment for major and minor failure & assessment of pain and parent satisfaction	T = 3 months
Intermediate Contact	Attrition prevention, update contact information, follow-up on pain	T = 4.5 months (Additional call reminder for Clinical Visit #3)
Clinic Visit #3	Reapplication of SDF in that group; Assessment for major & minor failure, radiographs*, and assessment of pain and parent satisfaction	T = 6 months

Intermediate Contact	Attrition prevention, update contact information, follow-up on pain	T = 9 months (Additional call for scheduling/reminder for Clinical Visit #4)
Clinic Visit #4	Assessment for major & minor failure, radiographs*, and final questionnaires	T = 12 months

*** Radiographs will be obtained only if an existing radiograph within 30 days of the visit is not available.**

7. Study Outcomes

7.1. Questionnaires + Acceptability Measures[31,32]

At the baseline clinical visit:

- *Pediatric Medical History Form*
    - Mott Children's Health Center/University of Michigan School of Dentistry Children's Clinic standard form
- *CRF 05 Baseline Parent Questionnaire* (Appendix 10, CRF 05)
- *CRF 06 Child Questionnaire* (Appendix 10, CRF 06)

When scheduled intermediate contact occurs via phone (or in person if presenting to MCHC/UMSOD for other reasons) at 1, 2, 4.5, and 9 months, the following form will be completed by the personnel making the contact, documenting the answers provided by the parent:

- *CRF 07 Intermediate Contact* (Appendix 10, CRF 07)

At recall visits (3 & 6 months, 12 month final recall, plus emergency visits) the parent and patient will complete:

- *CRF 08 Follow-up Parent Questionnaire* (Appendix 10, CRF 08)

OR

- *CRF 09 6 & 12 Month Parent Questionnaire* (Appendix 10, CRF 09)
- *CRF 06 Child Questionnaire* (Appendix 10, CRF 06)

7.2. Clinical Variables

At the baseline visit the study teeth carious lesions will be assessed based on size (mm), dentin color (yellow, brown, black), dentin hardness (soft - any explorer penetration of dentin when very light force is applied or hard – no dentin penetration when using an explorer with very light force[21]), and periapical radiographs (outer/middle/inner third of dentin, major/minor failure criteria). All information will be noted on the respective *CRF Intervention Visit* by the provider prior to treatment. These clinical characteristics will also be recorded for the SDF groups at follow-up visits (as the lesion is exposed clinically). Recall clinical visits will involve assessment of the lesion based on minor and major failure criteria (Table 2). All assessments will be noted on the respective *CRF 3 & 6 Month* (Appendix 10, CRF 10 & 11) or on the *CRF 12 Month* at the patient's 12 month recall (Appendix 10, CRF 12 & 13). Both groups will have periapical radiographs taken at the baseline and 6 and 12 month recalls (and at any other time if deemed clinically necessary). If a radiograph from within 30 days of the visit is available, a radiograph will not be taken at the study visit unless deemed clinically necessary. De-identified clinical photos will also be taken as deemed necessary for research and publication purposes, with parental consent. Length of time and cost for each intervention will be calculated and analyzed for comparison.

Table 2. Major and Minor Failure Criteria[30]

	SDF Application	Conventional Restoration
Success	• Caries arrested – dentin feels hard to explorer • No clinical signs or symptoms of pulpal pathology • Tooth exfoliated without major or minor failure	• Restoration appears satisfactory • No clinical signs or symptoms of pulpal pathology • Tooth exfoliated without major or minor failure
Minor Failure	• Caries progression – soft dentin, increase in lesion size clinically or radiographically • Reversible pulpitis to be treated without pulpotomy or extraction	• Secondary caries • Restoration fracture or wear requiring repair • Loss of restoration • Reversible pulpitis to be treated without pulpotomy or extraction

Major Failure	• Pulpitis requiring pulpotomy or extraction • Abscess formation • Caries progress to the extent that tooth is unrestorable	• Pulpitis requiring pulpotomy or extraction • Abscess formation • Restoration loss leaving tooth unrestorable

7.3. Providers:

Dentists'/pediatric residents' preferences for the 2 treatment options and time needed to complete a baseline visit will be recorded for each of the 2 interventions and logged on the respective *CRF Intervention Visit* (Appendix 10, CRF 02 & 03).

Provider preference of treatment modality cannot be collected through the clinical measurements on the study Case Report Forms. Therefore, collecting this data from the provider in addition to the clinical measurements will show feasibility and likelihood of future use. It would also be of great interest to the dental community.

7.4. Economic Measures

The economic evaluation of the two treatment strategies will be based on the time and material-based cost which will be calculated with the assistance of a Masters of Public Health student.

Additionally, this study offers the potential opportunity for continued research in long-term recalls and histological analysis of the study teeth upon exfoliation.

8. Retention Strategy for Participants

Mott Children's Health Center serves children and families 200% of the poverty level and below. While the children are receiving care at Mott Children's Health Center and the University of Michigan School of Dentistry, their parents, however, are not. The intention of this study is to assess the effect of SDF, yet we are very interested to promote oral health (which in the case of young children is very dependent on family health), so we will seek a study participant fee to

account for transportation costs to study visits and funds that can be used for assistance with the oral health care needs of any family members of the study participants, if necessary. Parents will receive $50 for their child's participation in the intervention appointment. Following successful recall contacts, the parents will be provided with a $10 reimbursement (this has been used very successfully by members of the study team in an NIH study to increase retention over time[33]). Parents will receive payment for each of three clinical recall visits: $60 at 3 months, $70 at 6 months and $80 at 12 months. Following initial intervention ($50), four recall contacts ($10 each) and three recall visits ($210 total) this will result in a total possible participation fee of $300. All payments will be provided in the form of a gift card, and given to the parent of a participant. The parent will acknowledge receipt. Payments are funded by Delta Dental, study sponsor, and are in no way funded by Mott Children's Health Center or the University of Michigan School of Dentistry.

9. Withdrawal Procedures

Subjects will have the right to withdraw at any time. Alternative conventional treatment can also be provided to the SDF group at any time, if it is believed by the provider to be in the patient's best interest. Reasoning will be recorded, as a preference for or against one treatment arm may provide further information as to public acceptance of a treatment, and these subjects will be withdrawn, *CRF 04 Treatment Deviation* (Appendix 10, CRF 04) and appropriate additional forms will be completed and the parent will receive a *Study Completion or Disenrollment Letter* (Appendix 11). Although no adverse events are expected *CRF 15 Unanticipated Problem* & CRF 16 *Adverse Event Logs* will be available if necessary (Appendix 10, CRF 15 & 16). In the event that the protocol is ever deviated from (ie. Missed recall or appropriate study procedure not completed) a *CRF 14 Protocol Deviation* (Appendix 10, CRF 14) will be completed.

10. Statistical Analysis

Power of the study will be fixed at 80% (β=0.20) just as was used in calculation for necessary sample size, with $\alpha = 0.05$ as the significance level. Data will be entered into SSPS Statistics or

another secured data collection system and data will be analyzed. Information will be stored on a password protected computer using an encrypted file and will be maintained as confidential protected health information (PHI). Examiners will be trained at the start of the study and calibrated on the use of the ICDAS criteria, and on the clinical outcome variables using extracted teeth to determine intra and inter-examiner reliability (dentin color, dentin hardness, and lesion size in mm), which will be measured with kappa statistics. A Chi-square test will be applied to determine if there is a difference in distribution of variables such as age, gender, brushing habits, fluoride exposure, etc. Chi-square tests will also be used to determine differences in dropout rates, failure rates, patient satisfaction/acceptance, and overall cost. The primary outcome, the proportion of children reporting major failures during the 12 month follow up period, will be analyzed using a mixed model with a binomial error structure. We will also analyze minor failures in a similar manner. The dependent variables will be a binary indicator of major failure, with differences between study treatments fitted as fixed effects. Estimates of the relative risk of major failure in the two groups will be presented in the form of odds ratios and associated 95% confidence intervals. Within this framework we will be able to estimate:

1. The mean difference between groups at the end of the follow up period;
2. The mean difference between groups across the whole of the follow up period; and
3. The difference in the rate of change of the outcome across the follow up period

11. Potential Limitations

An initial potential problem in the study may be to obtain the 98 patients needed per the power analysis calculation. Hopefully this will not remain too much of an obstacle, as children are frequently seen at Mott Children's Health Center and University of Michigan School of Dentistry Children's Clinic with carious lesions of this nature. When enrolling in this study, parents are either simply enrolling their children in a study where they would be provided the care that they would otherwise be provided outside of the study or, if receiving the alternative SDF treatment, they always have the ability to opt out and receive their definitive, conventional treatment. At the completion of the study, children who received care in the SDF group will have their study teeth restored according to AAPD guidelines or monitored for exfoliation, whichever is deemed most appropriate by their final provider or elected by the parent.

In order to prevent confusion and withdrawal from the study following intervention due to misinformation, all residents at Mott Children's Health Center and the University of Michigan School of Dentistry Children's Clinic who are providers for this study will be standardized in terms of the presentation of the study to the parents and patients and in the informed consent and assent process for the parents and children involved. It is important that these patients and their parents understand especially how the tooth may look following treatment. Teeth treated with SDF may become darker, and it is important to standardize this presentation by all residents so that patients are not withdrawing from the study simply because they were unaware of these anticipated consequences of the treatment.

In order to achieve a sample population of this size in such a short amount of time, five or six residents at each clinical site will be completing the screening, treatment, and recall of these patients. While having many providers is a limitation of the study, all providers will be trained and calibrated in their assessment of the tooth color and hardness as well is in their SDF application technique.

As with any treatment provided in children, especially those as young as two, it is possible that the children may be uncooperative for their appointments and that recall procedures cannot be performed. If a complete recall procedure cannot be fully completed, it is possible to simply complete the portions of the recall that are able to be completed safely. Children who cannot complete an intermediate clinical recall visit but still wish to remain in the study will be continued to be monitored until the final study visit, and the reason for failure to complete the recall will be noted.

Finally, given the socioeconomic status of these patients, it may be difficult for parents to miss work as well as arrange transportation to and from appointments. For this reason, it was determined that study participants will receive a study participant fee to help offset transportation costs and to hopefully additionally assist with any other oral health care needs of the patient's immediate family if necessary.

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