NCT Title:	**Clinical Trial Proximal Caries Infiltration and Detection**
NCT Number:	NCT01796106
IRB Approval Date:	02/06/2015

Content:

Study Protocol

Title:	**Clinical Efficacy of Caries Infiltration (Icon) – A Randomized, Blinded and Controlled Pilot Study of Early Caries Progression Detection**
Short Title:	Clinical Trial proximal Caries Infiltration and Detection
Running Title:	**DETECT13**
Protocol-ID:	NCT01796106
Sponsor:	DMG Dental Material Gesellschaft mbH Elbgaustraße 248 22547 Hamburg
Study Site:	The Center for Pediatric Dentistry 6222 NE 74th St Seattle, Washington 98115 United States
Version:	StudyProtocol_NCT01796106_V6[redacted]
Replaces Version:	StudyProtocol_NCT01796106_V5[redacted]
Date:	13 February, 2015

[redacted]

Content

1 Synopsis of the Clinical Investigation

1.1 Description of the CIP

The objectives of the Clinical Investigative Plan (CIP) are to provide a full description of the planned clinical trial. The preceding short narrative (Synopsis) introduced the goal of the project and its approach to investigate the clinical efficacy of management of early caries lesions by resin infiltration, which may be imaged through a SFE laser optical device comparable to radiographic results.

1.2 Sponsor

DMG

Dental Material Gesellschaft mbH

Elbgaustraße 248

22547 Hamburg

GERMANY

www.dmg-dental.com

+49 40 840 060

[redacted]

1.3 The Study Organization

The trial organization is located at The Center for Pediatric Dentistry, Seattle, Washington, US. The designated research team will conduct clinical studies to investigate results of alternative treatment options for dental caries.

This team includes [redacted]

Contact details and responsibilities are listed in 21.1.

[redacted] is a world-renowned Pediatric Dentist and expert on early caries. [redacted] will provide oversight and leadership on this study as the Principal Investigator. [redacted] has broad experiences in clinical research being engaged in patient-oriented research for years. She will be the Co-investigator and the main contact for study communications (clinical site).

The study is encouraged by DMG Dental Material Gesellschaft mbH, thereafter named “sponsor”. The sponsor will provide comprehensive support during study design, implementation and post processing by notified study contacts.

The study contacts [redacted]

take responsibility for monitoring the clinical trial and ensure proper supervision of all study belongings. Contact details and responsibilities are listed in 21.2, 21.3 and 21.4.

1.4 Abstract

Introduction: Research efforts using Icon have been in regard to its efficacy on treating early caries and white spot lesions. It has been found by numerous studies to be an effective form of treatment on stopping caries before traditional restorative work needs to take place. [redacted]

Objective: The hypothesis to be tested is that Icon performs similarly to an established prevention strategy for early caries (Oral hygiene instruction and topical fluoridation) for caries arrest; and caries progression may be imaged through a SFE laser optical device.

Materials and Methods: We propose a [redacted] study of Icon vs. control (Oral Hygiene Instructions [OHI]) and topical fluoridation) for early caries arrest in primary molars. Lesion depth will be performed through standard-of care methods, i.e. radiographs and visual exams, plus a novel optical device based on scanning fiber endoscope (SFE) technology for laser light imaging for early caries detection in pediatric populations. We will utilize SFE laser optical device prototypes developed by the University of Washington's Human Photonics Lab (HPL), a device already in human use for other applications, including imaging and cancer screening.

Clinical Significance: This controlled trial will assess the positive effects of [redacted] infiltration by ICON and may open a new therapeutic strategy in pediatric dentistry. Additionally, this study would be one of the first in vivo dental applications of the SFE optical device, and would add a novel early caries visualization technique to the armamentarium for detecting caries progression.

2 Description and Properties of the Medical Device to be investigated

2.1 Icon Kit for caries infiltration

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

2.2 Chemical Composition

2.2.1 Chemical Composition Infiltrant (Resin)

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.2.2 Chemical Composition Ethanol Solution (Dry-it)

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

2.2.3 Chemical Composition HCl Etching Gel (Hydrochloric Acid Gel)

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.3 Instructions for use

[redacted]

[redacted]

[redacted]

[redacted]

3 Objectives of the Clinical Investigation Plan (CIP)

The objectives of the CIP are to provide a full description of the planned clinical trial. The preceding short narrative (Synopsis) introduced the goal of the project and its approach to investigate the clinical effectiveness of management of caries lesions by resin infiltration.

The Background and Rationale section addresses the relevance of the project to oral health and rationale for the proposed project. The existing knowledge is briefly stated, including literature citations and highlights of relevant data, indicating the gap that the project is intended to fill.

The research plan includes the Study Design and Methods addressing the hypotheses to be tested, followed by Specific Aims. The data collection and analysis (including assessment of statistical significance) will be described and used to prove or disprove the hypotheses.

Previous experience with the material involved is described including attention to risk analysis. Expected results, potential difficulties and limitations are discussed and solutions or alternative approaches are indicated.

4 Preliminary Investigations and Justification of the CIP

4.1 Background and Rationale

Icon, by DMG, is a caries infiltration system developed to arrest early caries rather than drill, fill or "wait and see." Icon is used as a restorative therapy for caries lesions thought of as too early for conventional restorative treatment. Icon prevents lesion progression and increases life expectancy for the tooth by establishing a diffusion barrier which prevents cariogenic acids from breaking down tooth structure and causing further demineralization. This barrier also serves to help maintain the mineral content of the dentition by blocking mineral content from leaching from the tooth. Icon is also an aesthetic treatment for white spot lesions by allowing the white spot to take on the appearance of the surrounding healthy enamel.

White spot lesions occur when the sub-surface porosity of the lesion fills with an air/fluid mixture thus changing the way light is refracted.[4] This change in refractive index causes the tooth to appear milky, yellow or brown in color and can also diffuse in streaks across the teeth. These discolorations can also be caused by excessive exposure to fluoride during development, also known as fluorosis. White spots, or areas of demineralization, often indicate early caries lesions and there are currently a few treatments to prevent further acid damage.

Current alternative forms of treatment for early caries include the following: 1) microabrasion, 2) fluoride treatments, and 3) sealants/commercial adhesives. Microabrasion tends to be used more for cosmetic purposes, and unlike Icon, is not used to arrest caries. A study on eight orthodontic patients with white spot lesions found that using microabrasion improved the cosmetic appearance of these lesions.[23] However, the authors suggest that this treatment is far from standard-of-care and there should be further research into the effects of microabrasion on loss of enamel and tooth structure.

Studies involving the topical application of fluoride to early caries lesions have demonstrated high rates of caries prevention, arrest, and/or reversal effectiveness, in both children and adults.[14] Although full mineral recovery might be achieved through such measures, in the case of shallow enamel lesions, the same treatment in deeper white spot lesions have demonstrated negligible remineralization effects.[36] Furthermore, the esthetic effect on white spots is often not corrected with the application of fluoride treatments; and thus, defeating one of the main purposes of treating white spots or areas of demineralization.

The use of sealants or commercial adhesives to halt the progression of early caries has also been researched. However, these studies have shown that these materials are unable to fully penetrate the lesion, leaving potential for further demineralization.[22] To prevent progression, it was necessary to treat the area deeper than just the immediate surface area, which these products are unable to do.

Icon is unique in that it can penetrate deeper into the tooth to arrest caries progression. Also, unlike the other treatment options discussed previously, it works on both halting caries progression as well as diminishing white spots/demineralization area appearance for better esthetics results.

In vitro and in vivo studies have been done on the treatment of caries lesions with resins such as Icon. A number of studies were found in which Icon by DMG was used to evaluate the effect on these lesions. Each of the studies reviewed verified that Icon can be used as a restorative treatment for early caries and white spots.[25] Another study evaluated Icon's application time on penetration of enamel caries. This study found that three minutes was a sufficient time for the Icon to penetrate caries lesions.[20]

From an aesthetic standpoint, Icon was found to be an effective treatment in masking white spot lesions.[31] This in vitro study monitored the effect of Icon on white spots over an eight week period. Icon had a significant effect on returning the subjected teeth to their natural color, whereas the fluoride toothpaste and gel applications did not.

Current standard-of-care for early caries detection relies on visual examinations with tactile sensation, aided by radiographs. Typically an explorer is used to determine enamel surface hardness, and visual clues such as color and translucency are relied upon to evaluate the caries status of a patient. The methodology is unsophisticated and fails to differentiate between varies stages of caries progression. In a study of 12 year old children with caries, it was found that the visual/tactile method, with or without diagnostic adjuncts, can diagnose cavitated lesions efficiently, but not non-cavitated carious lesions.[3] Furthermore, visual-tactile techniques are known to be unreliable due to subjectivity. Lesions can go undetected because teeth are typically examined by the naked eye, and there is need for supplemental analysis when faced with clinical signs that will leave a dentist uncertain, including dark occlusal or approximal shadows.[15] Caries detection through radiograph examination is problematic because it is a flawed imaging system; and caries is detected after it has progressed through enamel and/or dentin. [9, 17]

The last 2 decades have seen various technological advances developed toward visualization and evaluation of caries. These include quantitative laser or light fluorescence (QLF), electrical conductance measurements (ECM), infrared (IR) laser fluorescence, direct digital radiography and Digital Imaging Fiber-Optics Trans-Illumination (DIFOTI). The research and data supporting effectiveness of this technology are at different stages of development, but there is no gold standard for dental imaging devices thus far. [23]

The scanning fiber endoscope was developed at the University of Washington's Human Photonic Laboratory (HPL) over the past decade. A completely new imaging technology was developed to provide high-resolution imaging from a very small and flexible scope. By placing a sub-millimeter fiber-optic scanner and lens assembly at the scope tip, the number of pixels (picture elements) is no longer related to the number of camera sensor elements. The result is near HDTV resolution from a scope the size and feel of a single strand of cooked spaghetti, with production of real time color video-rate images with 600 X 600 line resolution using scanned low-power red, green, and blue laser light.

The ultrathin endoscope developed at the UW Mechanical Engineering Department has been applied to numerous biomedical areas such as esophageal cancer screening, bile duct imaging, and bladder surveillance. This threadlike imaging device is less than 1.5 mm in diameter and is highly flexible behind its short rigid tip, making it ideal for intraoral use in pediatric populations. (See Figure 1.)

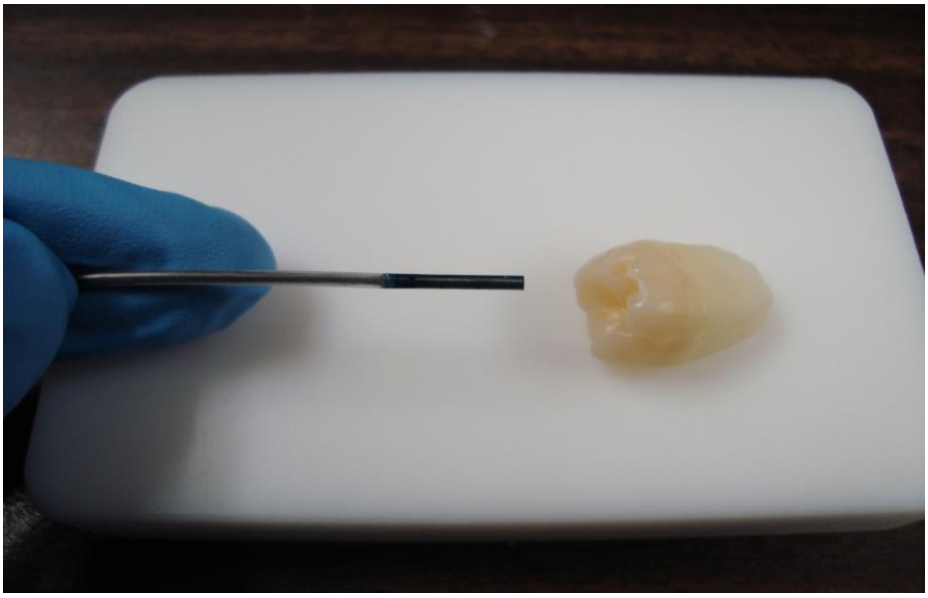


Figure 1: The ultrathin Scanning Fiber Endoscope (SFE) optical device is pointed toward the occlusal surface of an extracted human molar. The threadlike imaging device is less than 1.5 mm in diameter.

Following the trend for higher performance in low-cost lasers used in DVD players, a violet laser light source has been integrated into the system for detecting early stages of tooth decay. Enhanced surface detail of teeth is more apparent using violet 405-nm wavelength compared to red 635-nm wavelength illumination, as shown in monochrome images of the same tooth (See Figure 2).

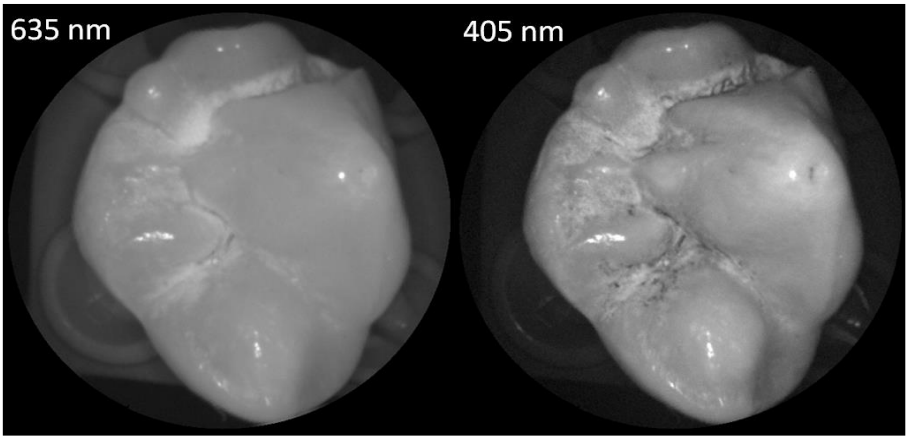


Figure 2: Monochrome images of the same tooth taken with red (635nm) and violet (405nm) laser light using the device in Figure 1.

The majority of visible light from conventional incandescent and natural light sources consists of wavelengths closer to the red 635-nm that penetrates more deeply into the tooth. Compared to images obtained at 635-nm, images captured using a violet light are not contaminated and blurred by superposition of light reflected from dental tissue at greater depths. Thus, 405-nm laser illumination of enamel surfaces of teeth produces enhanced image details. The ultrathin endoscope with short-wavelength illumination may be used to visualize surface manifestations of phenomena such as demineralization associated with early caries, thus better aiding the clinician for detection of tooth decay before caries progresses into cavitation.

Currently no single method for caries detection can be used on all tooth surfaces under all conditions. These diagnostic devices and methods lack sensitivity and specificity; with caries detection at a point when surgical or restorative intervention is required. Additionally, these optical imaging devices are cumbersome, and often lead to inaccuracy due to user failure. Ultimately, these approaches result in caries lesions diagnoses overlooked at the earliest stages when less invasive measures, including remineralization techniques such as Icon, may be effective. Clinical caries detection sensitive to early lesions would bring about innovations in treatment modalities through medicinal therapeutic and preventive approaches, including chemotherapeutic approaches such as Icon. An imaging system such as the SFE optical device, specifically designed for dentistry, would be the ideal approach.

4.2 Hypotheses

4.2.1 Hypothesis I

The hypothesis to be tested is that Icon performs similarly to an established prevention strategy for early caries (Oral hygiene instruction and topical fluoridation) for caries arrest.

4.2.2 Hypothesis II

Caries progression may be imaged through a SFE laser optical device.

4.3 Previous Experience with the Study Material

4.3.1 Description of the clinical procedure

The proposed components of the infiltration kit are substantially equivalent to a variety of currently marketed dental materials in terms of physical and mechanical properties. The *indication for use* of the DMG "Infiltration kit for caries lesions" is micro-invasive treatment of early approximal caries. The materials will be used according to the label.

4.3.2 Preclinical Testing

The materials to be used for infiltration (etchant and infiltrant) have received EEC market authorization for medical devices [redacted] Therefore, complete documentation of preclinical testing and biological evaluation of the device and its results has passed the appropriate regulatory bodies. Documentation and approvals are on file with the sponsor.

4.3.3 Previous Clinical Experience

The devices used in this study have seen clinical application for several years for infiltration indication with excellent results. The materials in the infiltration kit will be used according to label and for approved indication (micro-invasive treatment of early approximal caries). The materials have a low incidence of adverse events and no serious adverse events have become known.

The concept of caries infiltration applying the penetration of a low-viscosity resin into the porous lesion of enamel caries was proven on extracted teeth.[25, 39] Furthermore, the positive effect on white spot depletion was shown on artificial lesions.[25] This in vitro study monitored the effect of Icon on

white spots over an eight week period. Icon had a significant effect on returning the subjected teeth to their natural color, whereas the fluoride toothpaste and gel applications did not.

4.3.4 Clinical Studies

Infiltrating a caries lesion is a currently introduced strategy to strengthen damaged tooth structure and to reduce caries progression without any surgical intervention.[39-40] Management of early lesions by infiltrating instead of or postponing restorative treatment would have a great impact towards improving oral health care by means of its non-invasive nature. It will drastically lengthen the life-cycle of a tooth.[25] Infiltration would provide a simple and cost-effective management option with the least possible iatrogenic effect and diminished need for future re-treatment due to deteriorating of restoration margins.[41]

The promising in vitro results of caries infiltration on extracted teeth were underlined by different clinical trials. Several groups reported slower caries progression in infiltrated sites compared to controls: Radiographically obtained quantification reveals lesion progression in 16% of infiltrated sites compared to 53% for controls after one year and for 24% (infiltration group) and 62% (control) after two years. Recently, the three year follow-up data were published, reporting 32% progression for infiltrated lesion and 70% for controls in this split-mouth study.[42] Meyer-Lueckel et al. measured progression rates of 7% (infiltrated sites) and 37% (controls) after 18 month in young adults.[43] The currently available 3-year data of this study report 4% progression in infiltrated lesion and 42% for controls.[44] Ekstrand et al. aimed to assess the efficacy of resin-infiltrated lesions covered by fluoride varnish (FV) versus FV treatment only of proximal lesions on deciduous molar teeth in a one year split-mouth study. Radiographically, 23% of the test lesions and 62% of the control lesions had progressed, comparable to the aforementioned results in young adults. [45]

5 Device Risk Analysis and Assessment

5.1 Risk Analysis of the Medical Device

There is a minimal risk associated with the device itself and the procedures involved in its use, as identified by risk assessment and post-market experience of substantially equivalent materials, beyond the common risks related to standard dental treatment.

Definition: *Minimal risk is the probability and magnitude of harm or discomfort anticipated in the research and not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests [45 CFR 46.102(i)]*

The entire treatment in each aspect, including lesion size and location, all materials, equipment and techniques used, is part of regular daily life. Dentist visits, like in this study, resulting in caries detection, diagnosis and management by regular preventive regimen or sealant are not at all out of the ordinary. It is –alas- rather ubiquitous and a common part of daily oral health care provisions that our professions provides to the public. Therefore, the risk is NOT greater than routine dental practice. The care provided meets this definition of minimal risk.

The SFE technology has been used in multiple human applications safely and efficaciously. Therefore, there is low risk in use of the technology in the dental setting. The device was deemed to be a non-significant risk device by the FDA. If a child expresses dismay or stress during the SFE imaging process, the participant will be withdrawn from further study participation.

5.2 Risk Management of the Clinical Device

Although the exclusion criteria mention allergy to methylmethacrylate (a commonly used monomer as a component in many commercial medical, dental, and non-medical applications), this allergy has a low prevalence and materials containing methylmethacrylate or its analogues are managed routinely in dental practices around the world every day. In the case of the rare occurrence of an allergy, patients are isolated immediately from contact, treated using well-known emergency procedures, and recover quickly. In almost every case, a patient knows in advance that they have these types of allergies because they must avoid contacts with a huge number of acrylic materials present normally in world as parts of garments, containers, and common household items. No other adverse effects are known, and none are anticipated.

6 Objectives of the Clinical Investigation

6.1 Objectives

The main purpose of the present study is to evaluate the efficacy of a low viscosity resin (Infiltrant; DMG, Hamburg, Germany) in controlling the regression of White Spot lesions. As a secondary purpose, this study intends to evaluate the usage of SFE for investigation of penetration success and for visualization of early caries.

6.2 Specific Aimes (Primary Endpoints)

6.2.1 Specific Aim I

- Caries arrest evaluated by bitewing radiographs

6.2.2 Specific Aim II

- Confirm optical measurements from SFE laser device correlate with clinical measures

6.3 Secondary Endpoints

- White spot reversal
- Secondary caries
- Post-operative sensitivity
- Color match / surface staining
- Surface quality / texture
- SFE for visualization of early caries and lesion depth assessment

6.4 Study Overview

We propose a randomized, blinded, clinical study of Icon vs. Control (Oral Hygiene Instruction [OHI] and topical fluoridation) as early caries interventions for caries arrest in pediatric populations. 50 non-cavitated early caries lesions, or areas of demineralization, in proximal surfaces of primary molars will be enrolled in this study. Up to 2 early caries lesions may be enrolled per patient, providing the second lesion is in a separate quadrant. Early caries lesions with demineralization seen on occlusal surfaces will be excluded from participation, along with white spot lesions from hypoplasia or fluorosis.

7 Design of the Clinical Investigation

The study will be designed as a controlled, randomized, blinded trial following CONSORT[42] recommendations as a single center study to investigate the effect of caries infiltration as an alternative treatment option for approximal caries lesions.

7.1 Clinical Investigation Protocol

Study enrollment phase includes patient interviews, dental screening and bite-wing radiographs taking.

7.2 Participant Selection

Individuals will be selected among the children who come to the Center for Pediatric Dentistry Seattle, Washington, USA for dental treatment. Healthy children between 6 and 13 years old, presenting at least one pair of early carious lesions in primary molars.

7.2.1 Inclusion Criteria

Children ranging in age from 6-13 years will be eligible to participate. The patients must have a one early caries lesions present in primary molars. Up to 2 early caries lesions may be enrolled per patient, providing the second lesion is in a separate quadrant . All patients must be in good general health and free of any systemic disease or disability, preventing any unnecessary procedures. Patients must be available, as well as can be anticipated, for one-year, and two-year recalls.

Criteria used to assess teeth for acceptance into this study include: (1) teeth fully erupted, in functional occlusion and (2) radiographic evidence of early caries in interproximal areas (1 or 2, Ekstrand's criteria[9]). The patients will be appointed for a pre-study appointment after the legal guardian has undergone the informed consent process for the patients to take part in the study.

Selected teeth will be dried for at least 5 seconds with compressed air and study lesions examined under a standard operating light in the CPD clinic. Visual exam: Ekstrand's criteria[9] will be used to evaluate and record (Table 8.4.2.1). Study lesions scored in categories 1 or 2 from Ekstrand's criteria will be enrolled in the study.

For radiograph examinations the DMG's criteria[7] will be used to evaluate and record carious lesions. Study lesions scored in categories E1 and E2 from DMG's criteria[7] will be enrolled in the study (Table 8.4.2.2 and Figure 3).

7.2.2 **Exclusion Criteria**

Patients will be excluded from the study if they are currently enrolled in a study that includes evaluation of other restorative materials or systems involving posterior teeth. Patients will be excluded if they have a documented history of any adverse reaction to clinical materials of the type to be used in the study; is an irregular dental attendee; exhibits sensitivity in test teeth during screening visit; and the study teeth are thought to have poor access. Early caries lesions with demineralization seen on occlusal surfaces will be excluded from participation, along with white spot lesions from hypoplasia or fluorosis. Patients refusing radiograph exam will also be excluded from the study as well as pregnant female participants.

8 Clinical Evaluations

8.1 Baseline Records (*Radiography)*

Additional radiographs will not be taken for purpose of the trial only, they will be performed as part of standard of care. The policy described below reflects the widely accepted, current best practice regarding detection, diagnosis and monitoring of approximal lesions. Standardized diagnostic bitewing radiographs will be taken using an aiming device. The device facilitates optimal direction of the x-ray beam and thus leads to optimal diagnostic representation of the caries lesion.

Radiographic evaluation of the lesions and the quality of the adjacent enamel contact surface by standardized bitewing radiographs at baseline will be used to detect and diagnose the caries and monitor lesion change. An extensive review of the scientific evidence supports the importance of initial bitewings and radiographic recall examinations for description of caries progression.[49-53] Both, the guidelines by Pitts and Kidd 4 widely used in Europe, and the ADA/FDA-coordinated guidelines [54] advise that in high risk children (age 10-16) the interval should be 6-12 month. The proposed timing of bitewings in our study (baseline and at yearly intervals) falls well within these guidelines. They rather represent a minimum of the advised frequency for a caries-prone study population of adolescents and young adults in the age range of 6-13 years.

8.2 Clinic visits

A trained study clinician will perform all standard clinical assessments of study lesions in groups 1 and 2, including visual exam and radiograph exam. The study clinician will provide Icon treatment to all study participants randomized to study arm 1 after the radiograph and visual exam. The study clinician will provide oral hygiene instruction and topical fluoridation therapy (Duraphat fluoride varnish) to all study participants randomized to study arm 2 after the radiograph and visual exam.

A trained study clinician will capture the SFE laser optical device image of the study lesions from all study participants. The study examiner will be trained and calibrated by the HPL research team prior to start of study. SFE laser optical device image diagnoses from baseline will be compared to diagnoses from radiograph and visual exams from chart review from the same visit.

Table 8.2 Overview of the procedures during each visit

Procedure	Screening visit	Baseline and Intervention	12 Month Follow-up	24 Month Follow-up
Time		D-0	M 12 (± 3 m)	M 24 (± 3 m)
Patient information	x			
Oral examination	x		x	x
Informed consent	x			
Medical history	x			
Inclusion and exclusion criteria	x		x	x
Selection of eligible lesions	x			
Caries risk assessment	x			
Placing ortho spacers(tx group) D-21 to -7 prior to BI		x	x	x
Randomization	x			
Radiographic examination		x	x	x
Examination by SFE Before spacers placed	(x)*	x		
Examination by SFE Before & After Icon placed		x	x	x
Examination by SFE		x		
Visual Assessment of lesion		x	x	x
Intervention (Infiltration) (EXPERIMENTAL)		x		
Instruction for oral health care		x	x	x
Record of adverse effects		x	x	x
Fluoridation (CONTROL)		x	x	x

*Can be done at screening or baseline appointment

8.3 Evaluation Categories

8.3.1 History Taking (Interview)

- Oral Health care behavior

8.3.2 Diet

- Snacking: frequency and content
- Softdrinks: frequency and sipping

8.3.3 Local Ecology

- No other scores will be documented

8.3.4 Caries Experience

- Ekstrand´s criteria
- Additionally, the caries experience and caries risk shall be recorded for each patient in the caries activity form supplied by DMG.

8.3.5 Individually standardized record (*Radiographs*)

- DMG criteria for Icon treatment

8.4 Evaluation Criteria

8.4.1 Preamble

None

8.4.2 Eligibiltiy Criteria

To be eligible for the study, each participant must meet preliminary eligibility criteria and the participant and the guardian must be willing to sign a statement of informed consent. This will document the agreement of the participant to participate in the studies activities.

Additionally, participants will be asked by study personnel not to participate in any other therapeutic research studies during the participant´s follow-up period from baseline to the 24 month visit.

Table 8.4.2.1 Ekstrand´s criteria for visual examination and evaluation of carious lesions

0	No or slight change in enamel translucency after air drying (5 s)
1	Opacity (white) hardly visible on the wet surface, but distinctly visible after air drying
2	Opacity (white) distinctly visible without air drying
2a	Opacity (brown) distinctly visible without air drying
3	Localized enamel breakdown in opaque or discoloured enamel and/or greyish discolouration from the underlying dentine
4	Cavitation in opaque or discoloured enamel exposing the dentine beneath

Table 8.4.2.2 Criteria used in the radiograph examination

E1	Radiolucency confined to the outer half of enamel
E2	Radiolucency involving the inner half of enamel
D1	Radiolucency in the outer third of dentin
D2	Radiolucency in the middle third of dentin
D3	Radiolucency in the inner third of dentin

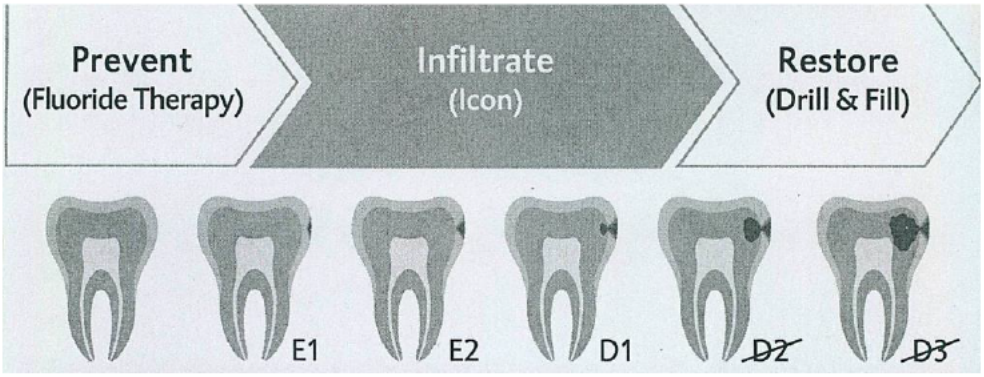


Figure 3: DMG criteria for treatment planning for Icon infiltration therapy. Adopted from (7).

NOTE: For study purposes only we will use criteria in E1 and E2 only.

8.4.3 Local ecology

- none

9 Clinical Measurements and Procedures

9.1 Screening Visit

The screening phase allows confirmation of subject eligibility for the trial based in inclusion and exclusion criteria. Screening includes patient information, eligible lesions are evaluated by a study investigator and randomly selected for treatment.

Upon successful completion of the informed consent process by a parent/legal guardian, the participant will be enrolled in the study and randomized to an intervention group. Both groups 1 and 2 will return to clinic 2 weeks prior to intervention baseline visit for a pre-study visit. During this visit orthodontic spacers will be placed interproximally in the study lesion area between the primary molars. The spacer will be maintained in the interproximal area until the patient returns for the intervention baseline visit. The spacer is non-invasive and placed to separate the teeth for better access during the intervention baseline visit for improved visualization and access for Icon/fluoride application. Once the spacer is removed the space will close naturally within 3-4 weeks.

9.2 Selection of Lesions (Screening visit only)

Study participants will be recruited from the Resident Clinic at the Center for Pediatric Dentistry at new patient or non-invasive recall visits. Resident clinicians and the research team will assist recruitment by identifying potential candidates with appropriate interproximal early caries lesions. All participants will be in general good health, aged 6-13 years, and enrolled into the study upon successful completion of the informed consent process.

9.3 Randomization

25 non-cavitated early caries lesions will be randomly assigned, using a random numbers table, to study arm 1) the Icon treatment group; and 25 non-cavitated early caries lesions will be randomly assigned, using a random numbers table, to study arm 2) the Control group (OHI and topical fluoridation).

9.4 Intervention Visit

9.4.1 Intervention Site "TREATMENT"

All groups will undergo visualization of lesions with radiograph exam, visual exam, and SFE laser optical device exam. 2 weeks prior to the SFE laser optical device exam orthodontic rubber spacers will be inserted next to the study lesions to separate the proximal space for better visualization. The initial SFE exam will occur prior to tooth separation at this visit.

Prior to Icon placement, SFE laser optical device will be performed. The study clinician will provide Icon treatment to all early lesions randomized to study arm 1 after the radiograph and visual exam and a post SFE laser optical device will be performed. The test lesions will be treated using Icon (DMG, Hamburg, Germany) following the instruction for use.

9.4.2 Intervention Site "CONTROL"

The study clinician will provide oral hygiene instruction and topical fluoridation therapy (Duraphat fluoride varnish; Colgate Oral Pharmaceuticals, New York, NY, United States) to all study participants randomized to study arm 2 after the radiograph, visual exam and SFE Laser Exam. The initial SFE exam will occur at this visit.

Topical fluoridation treatment will be provided is varnish (Duraphat) per manufacturer's instructions.

9.5 Follow-up Evaluations

Follow-up assessments will occur at months 12 and 24 from baseline +/- 3 months. Study patients will be reminded of their follow up visit. The following will occur at all follow-up visits:

- Two weeks prior to the appointment (-21 to -7 days) Orthodontic rubber spacers will be inserted next to the iconized lesions to separate the proximal space for better visualization.
- Radiograph exam of study lesion
- Visual exam of study lesion
- SFE laser optical device imaging of study lesion

Results are documented in CRF (Appendix A1).

If study lesions are noted to be progressing at any point the study clinician will refer the participant for standard-of-care treatment to the CPD Resident Clinic. Progression is defined as lesion changes

from E2 to D category according to DMG's criteria. The study participant will no longer participate in the study at this point.

9.6 Concomitant Treatment

The clinical study is concerned with no more than 2 lesions per patient. Within the study no additional concomitant treatment will be offered to the subjects outside the normal local clinical routines. At the recall appointments, normal recall procedures will be applied.

10 Data Management

10.1 Data Management Plan

10.1.1 Data collection

Data collection is done using the CRF that exists in the form of a paper version. The method is to employ paper CRFs to collect the data responses, which are subsequently translated to the monitoring database. These paper CRFs are filled up by the investigator according to the protocol.

10.1.2 CRF tracking

The entries made in the CRF will be monitored by the designated DMG clinical monitor for completeness and filled up CRFs are entered into the database. CRFs are tracked for missing pages and illegible data manually to assure that the data are not lost. In case of missing or illegible data, a clarification is obtained from the investigator and the issue is resolved.

10.1.3 Data validation

Data validation is the process of testing the validity of data in accordance with the protocol specifications. Discrepancy is defined as a data point that fails to pass a validation check. Discrepancy may be due to inconsistent data, missing data, range checks, and deviations from the protocol. Ongoing quality control of data processing is undertaken by the monitor at regular intervals during the course of clinical trial.

10.1.4 Discrepancy management/query resolution

Discrepancy management includes reviewing discrepancies, investigating the reason, and resolving them with documentary proof or declaring them as irresolvable. Discrepancy management helps in cleaning the data and gathers enough evidence for the deviations observed in data. For discrepancies that require clarifications from the investigator, the monitor will discuss the query with the investigator or will be sent to the site. The Investigators will write the resolution or explain the circumstances that led to the discrepancy in data.

10.2 Data Quality Assurance

Data Quality Assurance is a critical phase in clinical research, which leads to generation of high-quality, reliable, and statistically sound data from the clinical trial. The clinical monitor is actively

involved in all stages of clinical trial right from inception to completion. For Data Quality DMG has implemented an adequate process knowledge that helps to maintain the quality standards of data management processes. Various procedures in Clinical Data Management including Case Report Form (CRF) designing, CRF annotation, monitoring database designing, data-entry, data validation, discrepancy management are assessed by the monitor for quality at regular intervals during a trial.

10.3 Data Privacy Protection

Electronic study files will be password protected and reside on a computer that is also password protected. Paper records will be maintained in a locked cabinet in a space that has locked entryways.

10.4 Study Database

Electronic study files as well as paper records, such as CRFs, will be collected and checked for completeness by the clinical monitor during the continuous on-site visits.

A carbon copy of the paper records will be stored at sponsor site. Moreover study data will be transferred into a monitoring specific database.

11 Biostatistical Design

11.1 Prospective Design

Controlled, randomized, blinded study, single center design.

11.2 Determination of Sample Size

50, non-cavitated early caries lesions, or areas of demineralization, in proximal surfaces of primary molars will be enrolled in this study. Early caries lesions with demineralization seen on occlusal surfaces will be excluded from participation, along with white spot lesions from hypoplasia or fluorosis.

11.3 Evaluation Strategy

The bitewing radiographs will be examined and assessed by evaluators for positive, none or negative change in size and density.

11.4 Statistical Analysis

11.4.1 Descriptive Statistics

Descriptive statistics (means, standard deviations, counts, and percentages) will be calculated for all variables. A Chi-square test of association will be performed to evaluate if there is a significant difference in caries arrest by treatment group at a significance level of 0.05. Additional Chi-square tests of association will be performed to determine if there is a significant association with the secondary outcomes by treatment group.

11.4.2 Blinding

Each subject enrolled into this study will be assigned a unique identifying code number. Every effort will be made to maintain the confidentiality of each study subject's identity. No presentation or publication of the study data will identify any study subject.

11.4.3 Evaluation of Records

SFE laser optical device image diagnoses from each time point will be compared to diagnoses from radiograph and visual exams from chart review from the same visit.

- For radiograph and visual exams: Assessments of caries lesions per standard of care will be abstracted from the electronic dental record system (Axium) and recorded on CRF.
- For SFE laser optical device image: Recordings from the device will be used to assess caries lesions and recorded on CRF.

11.4.4 Missing Data

Missing data due to dropouts have been accounted for in adjusted sample size. The missing data will be at random. Data of dropouts will be assigned as “last observation carried forward”.

11.4.5 Statistical Software

STATA Data Analysis and Statistical Software will be utilized to perform data analysis.

12 Method of Reporting

12.1 Periodic Reports to the Sponsor/Monitoring

Periodic reports will be given to the sponsor in line with the frequently held monitoring visits.

The activities/reporting by the monitor that take place during the on-site visit include, but are not limited to the following:

- Only subjects who meet the study eligibility criteria are enrolled
- Informed consent process was conducted appropriately and that informed consent will be obtained prior to proceeding with any study procedures
- Data was collected and analysed as specified in the protocol
- Adverse events were reviewed promptly and reported as required
- Privacy and confidentiality of subjects was maintained
- Documentation of dropouts
- Evaluation of primary and secondary endpoints
- During an annual visit, the Monitor focuses on the areas where the majority of the deficiencies were identified or addresses other problems or issues noted since the last visit.
- The Monitor identifies and reports any suspected fraud and scientific misconduct if discovered during the review.

The clinical monitoring process of the sponsor can be classified into the following periodical visits:

12.1.1 Study initiation visit

The monitor conducts the study initiation visit after the site submits the protocol to its IRB and in advance of study activation.

The study initiation visit is held at the study site. The monitor prepares a clinical study initiation visit report to document the study initiation visit. The PIs, Sub-Investigators, and Site Coordinators must be prepared to discuss the procedural as well as the scientific aspects of the protocol during the initiation visit.

12.1.2 Annual Monitoring Visit

The monitor schedules and conducts on-site monitoring visits. The first annual monitoring visit to the study site occurs 12 months after a study opens; then annually thereafter until study closure.

The monitor may conduct interim visits as requested. An interim visit can be conducted as a follow-up to an annual visit where a number of deficiencies were identified, or it can be requested for reasons such as the complexity of the study, staff changes, or number of subjects enrolled.

The annual visit is generally scheduled for two days. The monitor prepares a follow-up-monitoring report to document the visit.

12.1.3 Close-Out Visit

The monitor schedules the close-out visit. The close-out visit usually takes one full day. If accrual is exceptionally large, an additional day can be required.

The activities/assessments by the monitor during the close-out visit include, but are not limited to, the following:

- Complete any outstanding site monitoring tasks (e.g., regulatory review and/or review of participant records) through the date of study termination or completion;
- Confirm that the IRB has been informed of the study closure
- Ensure the PI understands follow-up requirements for reporting AEs for subjects who have completed the study
- Conduct a summary meeting with Study Principals to discuss findings and plans for resolution of outstanding issues

A final report will be prepared after finishing all monitoring activities.

13 Changes of the Clinical Investigation Plan

13.1 Amendments to the CIP

All amendments to the CIP shall be agreed to by the principal clinical investigator and be recorded with a justification for the amendments. Deviations will be reviewed to determine the need to amend the CIP or to terminate the investigation.

14 Deviations from the Clinical Investigation Plan (CIP)

14.1 Deviations from the Clinical Investigation Plan

Any deviation from the CIP will be documented together with an explanation for the deviation. Deviations will be reported to principal investigator who is responsible for analyzing the deviations and assessing their significance.

Other Reportable Information and Occurrences (ORIOs: such as protocol deviations, accidents/incidents, and complaints) will be reported to IRB in the form of an ORIO report:

- Within 7 days when urgent subjects safety or regulatory concerns exist and/or oversights letter is received
- Within 15 days when situations or event potentially alters risk-benefit assessment and/or may jeopardize integrity of study results and/or potential benefits to subjects
- With scheduled continuation review or concurrently with report to oversight body, whichever comes first, when ORIO falls outside of other IRB timeframe parameters

14.2 Withdrawal / Dropout of Subjects

Table 14.1.2 Withdrawal and drop-out of subjects separated by level, reason and consequences

Level	Cause	Consequence
Lesion	An allocated lesion progresses radiographically into the middle or inner 1/3 of dentin (criteria D2 and D3).	The lesion is treated invasively by removing the caries and placing a filling. The case is scored as "progressed" and "failure".
	The patient shows signs of reversible or irreversible pulpitis in an allocated tooth.	The tooth is treated. The case is scored as "progressed" and "failure".
Patient	The patient shows adverse reactions for one of the study materials.	Counteractive measures are taken. Unwanted effects are documented in CRF and CEF. The patient is scored as "drop out", data will be assigned as "last observation carried

		forward".
	The patient can not be examined (i.e. x-ray during pregnancy)	The patient is scored as "drop out", data will be assigned as "last observation carried forward".
	One or more allocated lesions have been treated by an external dentist.	The patient is scored as "drop out", will be assigned as "last observation carried forward".
	The patient can not be contacted to make appointments.	The patient is scored as "drop out".
	The patient decides to withdraw his informed consent or study participation.	The patient is scored as "drop out".
Study	One or more patient(s) show severe unwanted side effects to treatment.	Individual counteractive measures are taken. The study is halted.
	More than five patients show unwanted side effects to one treatment or material used.	Individual counteractive measures are taken. The study is halted.

14.3 Length of follow-up – Potential Study Extension

Based on the actual study design there is no extension planed. If obtained data indicate a necessity for follow-up investigations this issue will be discussed with the sponsor and documented in the study files.

15 Confirmation of Study Material Application

Application of study material will be documented in the Study Material Application form (Appendix A2) including patient ID, investigator, date of application, material batch number and signature.

16 Ethical Considerations

This protocol was approved by the ethical committee from the Center for Pediatric Dentistry, Seattle, Washington (Appendix A3). Parents or guardians will sign an informed consent. (Appendix A4). Operative dental treatment will be provided to the participants when necessary.

17 Relevant Standards and Guidelines

The Clinical Investigation Protocol for this study includes all components and documentation as required to conform to international standards for clinical research (CONSORT [46], ISO/DIN[47] and Good Clinical Practice Guidelines[48]).

18 Adverse Events

18.1 Adverse Events

An adverse event (AE) is defined as any unintended adverse experience associated with the study materials or study procedures that results in an unplanned medical assessment or treatment, or changes the risk to subjects. Any adverse reaction to the treatment provided as part of the study will be fully investigated and reported to the IRB. AEs will be reported according to the IRB defined timelines using appropriate forms.

All materials and devices used in this study have been approved by local regulatory bodies and are currently on the market in various parts of the world. Their clinical use is according to label. Therefore, no foreseeable adverse events are expected.

18.2 Serious Adverse Events

Emergency contact details for reporting of serious adverse events are included in the CIP (Appendix A5).

Serious Adverse Events are adverse events that:

a) led to a death,

b) led to a serious deterioration in health that either:

1) resulted in a life-threatening illness or injury, or

2) resulted in a permanent impairment of a body structure or a body function, or

3) required in-patient hospitalization or prolongation of existing hospitalization, or

4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

In case of a serious adverse event and subsequent need for un-blinding the name-code list can be assessed immediately and breaking the code will not cause any further problem. The data recorded until the report of adverse event will remain included in the dataset.

18.3 Report by the investigator to the sponsor

DMG has implemented and maintains a system to ensure that the reporting of the reportable events will be provided by the investigator to the sponsor in acceptable timely conditions using the Adverse Event/ Adverse Device Effect (AE/ADE) Report Form (Appendix A6).

18.4 Report by the sponsor to the National Competent Authorities

Reportable events will be reported at the same time to all National Competent Authorities where the clinical investigation has commenced.

- a SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than **2 calendar** days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
- any other reportable events or a new finding/update to it: immediately, but not later than **7 calendar** days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

19 Early Termination or Suspension of the Investigation

All materials and devices used in this study have been approved by local regulatory bodies and are currently on the market in various parts of the world. Their clinical use in this investigation is according to label. Therefore, early termination or suspension of the investigation due to problems with the restorative materials is not anticipated.

If the investigation is terminated prematurely or suspended, the principal clinical investigator will promptly inform the clinical investigators of the termination or suspension and the reason(s) for this.

The ethics committees will also be informed promptly and provided with the reason(s) for the termination or suspension by the principal clinical investigator.

If the results of Icon or Control failed or is found to be clinically unsatisfactory, the Principal Investigator will provide an alternative treatment (of a different tooth colored restorative such as a composite resin restorative and bonding system, or other direct restorative system, at the discretion of the clinician,) to the subject. The subject will then be discontinued from the study.

20 Publication Policy

The study investigator may present or publish the results of scientific investigation involving this study. Details are described in the study contract section 6 in detail.

21 Administrative Arrangements

21.1 The Research Team and its Responsibilities

Principal Investigator: [redacted]

Co-Investigator: [redacted]

Co-Investigator: [redacted]

Co-Investigator: [redacted]

21.2 Head of the Clinical study (Sponsor)

[redacted]

21.3 Regulatory Affairs/ Clinical Monitoring (Sponsor)

[redacted]

21.4 Clinical Study Contact (Sponsor)

[redacted]

21.5 Projected Time Frame

The clinical study will start as soon as the required ethical approvals have been received and Training has been provided to the clinical team. [redacted]

The time frame is summarized in table 21.5

Table 21.5 Overview of the study´s time frame

time	Study part
[redacted]	Study preparation – CIP and IRBs completed
[redacted]	Training of clinical team Clinical site preparation
[redacted] [redacted]	**Clinical study initiation** - Patient screening and enrollment - Clinical phase: screening and baseline sessions **Baseline report**
[redacted] [redacted]	One-year recall **One-year report**
[redacted] [redacted]	Two-year recall **Two-year report**
[redacted]	**Completion of two-year study- Final report**

21.6 Financing

Financial agreements regarding funding of the different aspects of the investigation are part of separate contracts between the Sponsor and the Research Team / The Center for Pediatric Dentistry, Seattle, Washington, US.

21.7 Reimbursement to Subjects

Subject compensation and incentives being part of the subject retention package for the clinical site will be part of a separate contract and fall outside the scope of the CIP.

21.8 Insurance of the Subjects

The study materials in this investigation are cleared by the governing bodies of the participating countries (US, Germany). Therefore, the subjects taking part in the trial are insured by the Sponsor against any injury caused by the study materials under investigation. If applicable, additional regulatory requirements in participating countries will be observed and are part of a separate contract.

21.9 Confidentiality

All unpublished information concerning this trail and the materials supplied to the principal clinical investigator and the investigators by the Sponsor will be treated confidentially by all parties involved until the sponsor gives written consents that the information may be published or handed over to third parties. The Sponsor has the rights on all data and information acquired during the investigation.

22 Appendices

[redacted]

[redacted]

[redacted]

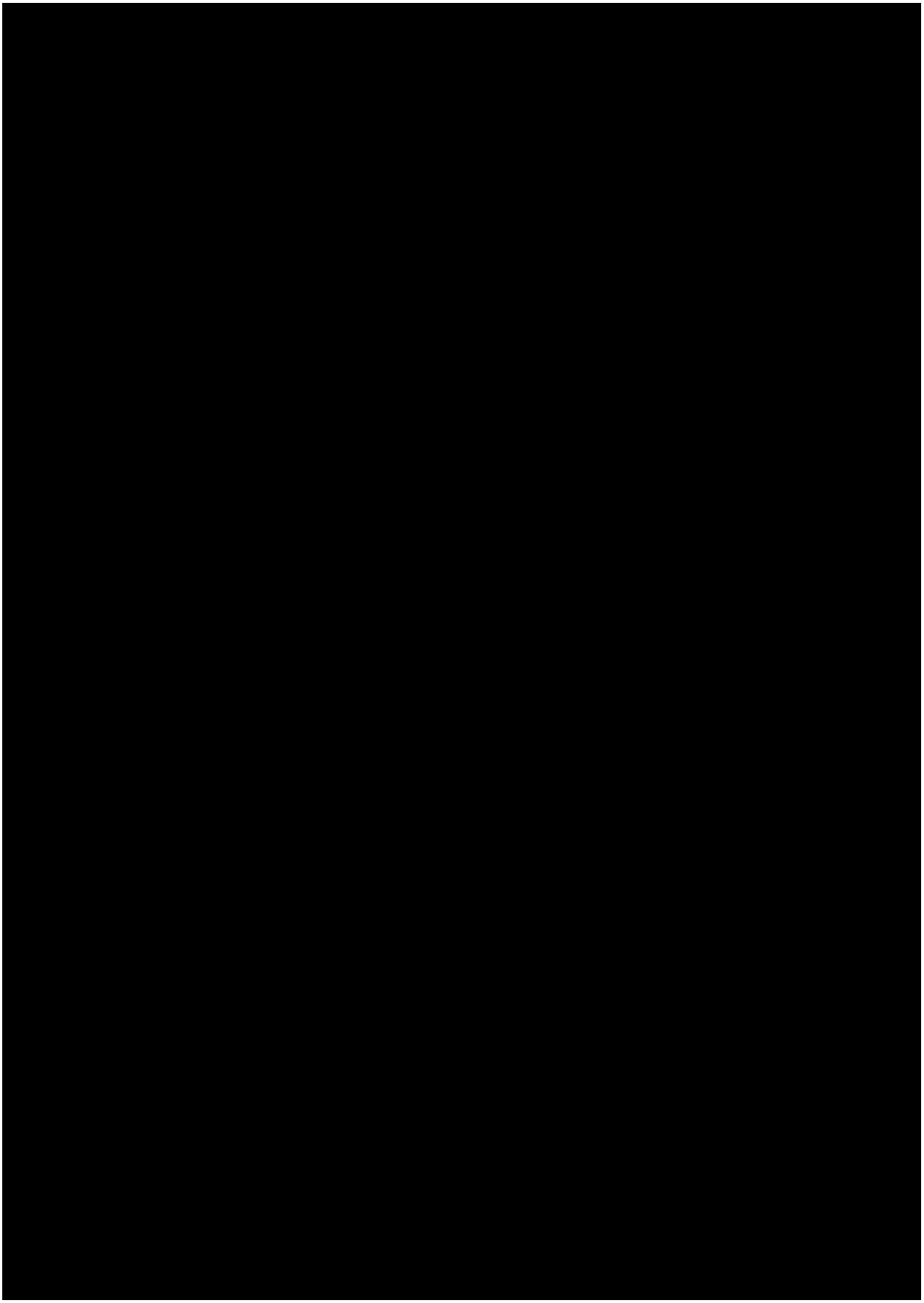
[redacted]

[redacted]

A2 Study Material Application Form

[redacted]

A3 Ethical approval



A4 Informed consent form

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

A5 Emergency contact information

In any case of emergency please contact:

[redacted]

and/or

[redacted]

A6 Adverse Event/ Adverse Device Effect (AE/ADE) Report Form

[redacted]

23 References

(1) Almeida AG, Roseman MM, Sheff M, Huntington N, Hughes CV. Future caries susceptibility in children with early childhood caries following treatment under general anesthesia. *Pediatr Dent.* 2000;22:302-306.

(2) Anusavice K. Management of dental caries as a chronic infectious disease. *J Dent Educ.* 1998 Oct 1998;62(10):791-802.

(3) Assaf, V., Meneghim, C., Zanin, L., Pardi, V., Pereira, C., and Ambrosano, M. Influence of diagnostic adjuncts to the measurement of caries prevalence at different caries thresholds. International Dental Journal. December 2003. Volume 53, Issue 6, p. 485-490.

(4) Belli, R., Christos Rahiotis, Edward W. Schubert, Luiz N. Baratieri, Anselm Petschelt, Ulrich Lohbauer, Wear and morphology of infiltrated white spot lesions, Journal of Dentistry, Volume 39, Issue 5, May 2011, Pages 376-385.

(5) Blank, M, Friedrich, M., Hamilton, J., Lee, P., Berg, J., and Seibel, EJ (2011) Laser scanning dental probe for endodontic root canal treatment, *Lasers in Dentistry XVIII*, Proc SPIE vol 7884, 788403-1-7.

(6) Delgado-Angulo EK, Bernabe E. Influence of host related indicators on dental caries in the permanent dentition. *Acta Odontal Latinoam* 2006; 19:85-92.

(7) DMG Icon Brochure. http://www.dmg-america.com/files/product/literature/[nid]/New_Icon_8pg_Brochure.pdf Accessed 02/15/2012.

(8) Du M, Luo Y, Zeng X, Alkhatib N, Bedi R. Caries in preschool children and it's risk factor in 2 provinces in China. *Quintessence Int* 2—7; 38:143-151.

(9) Ekstrand KR, Ricketts DN, Kidd EA, Qvist V, Schou S. Detection, Diagnosing, Monitoring and Logical Treatment of occlusal caries in Relation to Lesion activity and severity. An *in vivo* examination with histological validation. Caries Res 1998;32:247-54.

(10) Featherstone JBD, Duncan JF, Cutress TW. A mechanism for dental caries based on chemical process and diffusion phenomena during in-vitro caries simulation on human tooth enamel. *Archs Oral Biol* 1979; 24: 101-112.

(11) Featherstone JBD. Remineralization, the natural caries repair process-the need for new approaches. *International Conference on Novel Anti-caries and Remineralizing Agents,* held in Vina del Mar, Chile 2008.

(12) Goel A, Chawla HS, Gauba K, Goyal A. Comparison of validity of DIAGNOdent with conventional methods for detection of occlusal caries in primary molars using the histological gold standard: An *in vivo* study.J Indian Soc Pedod Prev Dent 2009;27:227-234.

(13) Gomes PR, Costa SC, Cypriano S, Rosaro de Sousa ML. Dental caries in Paulina, Sao Paulo, Brazil an World Health Organization goals for 2000 and 2010. *Cad Saude Publica* 2005; 20:866-870.

(14) Griffin, S.O., E. Regnier, P.M. Griffin and V. Huntley, Effectiveness of fluoride in preventing caries in adults. *Journal of Dental Research*, 86 (2007), pp. 410–415.

(15) Ismail AI. Visual and Visuo-tactile Detection of Dental Caries. J Dent Res 2004;83Suppl1:C56-C66.

(16) Ismail AI. Determinants of Health in Children and the Problem of Early Childhood Caries. *Pediatr Dent.* 2003;25:328-333.

(17) Ismail, A. Caries Process and Prevention Strategies: Diagnosis. http://www.dentalcare.com/en-US/dental-education/continuing-education/ce373/ce373.aspx?ModuleName=coursecontent&PartID=3&SectionID=-1. accessed Oct 04, 2011.

(18) Kagihara LE, Stark M. Assessment, management, and prevention of early childhood caries. *J Am Acad Nurse Pract* 2009; 21:1-10.

(19) Lee CM, Engelbrech CJ, Soper TD, Helmchen F, Seibel, EJ. Scanning fiber endoscopy with highly flexible, 1 mm catheterscopes for wide-field, full-color imaging. *J Biophotonics.* Jun 2010:3(5-6):385-407.
(20) Meyer-Lueckel, H., Chatzidakis, A., Naumann, M., Dörfer, C.E., and Paris, S., Influence of application time on penetration of an infiltrant into natural enamel caries, Journal of Dentistry, Volume 39, Issue 7, July 2011, Pages 465-469.
(21) Meyer-Lueckel, H., Paris, S., and Kielbassa, A.M. Surface layer erosion of natural caries lesions with phosphoric and hydrochloric acid gels in preparation for resin infiltration. Caries Res. 2007; 41(3):223-30.
(22) Mueller, J., H. Meyer-Lueckel, S. Paris, W. Hopfenmuller and A.M. Kielbassa, Inhibition of lesion progression by the penetration of resins in vitro: influence of the application procedure. *Operative Dentistry*, 31 (2006), pp. 338–345.
(23) Murphy, T.C., Willmot, D.R., and Rodd, H.D., Management of postorthodontic demineralized white lesions with microabrasion: A quantitative assessment, American Journal of Orthodontics and Dentofacial Orthopedics, Volume 131, Issue 1, January 2007, Pages 27-33.
(24) Paris, S., Meyer-Lueckel, H., Colfen, H.,and Kielbassa, A.M. Penetration coefficients of commercially available and experimental composites intended to infiltrate enamel carious lesions. Dent Mater. 2007 Jun;23(6):742-8.
(25) Paris, S., Meyer-Lueckel, H., and Kielbassa, A.M Resin infiltration of natural caries lesions. J Dent Res. 2007 Jul; 86(7):662-6.
(26) Paris, S. and Meyer-Lueckel, H. Caries inhibition by infiltrants in situ. Caries Res 43 (3): p. 228 (Abstr. No.136), 2009
(27) Reich E, Lussi A, Newbrun E. Caries-risk assessment. *Int Dent J.* 1999 Feb 1999;49(1):15-26.
(28) Rocha RO, Ardenghi TM, Oliveira LB, Rodrigues CR, Ciamponi AL. *In vivo* effectiveness of laser fluorescence compared to visual inspection and radiography for the detection of occlusal caries in primary teeth. Caries Res 2003;37:437-41.
(29) Sgan-Cohen HD, Mann J. Health, oral health and poverty. *J Dent Res Assoc* 2007; 138:1437-1442.
(30) Tinanoff N, Douglass J. Clinical decision making for caries management in children. *Pediatr Dent.* 9154;24(5):386-392.
(31) Torres, C., Borges, A.B., Sarmento Torres, L.M., Gomes, I.S., and Simões de Oliveira, R., Effect of caries infiltration technique and fluoride therapy on the colour masking of white spot lesions, Journal of Dentistry, Volume 39, Issue 3, March 2011, Pages 202-207.
(32) Tsai AI, Chen CY, Li LA, Hsiang CL, Hsu KH. Risk indicators for childhood caries in Taiwan. *Community Dent Oral Epidemiol* 2006; 34:437-445.
(33) Valera, B., Pessan, P., Valera, C., Mondelli, J., and Percinoto, C. Comparison of visual inspection, radiographic examination, laser fluorescence and their combinations on treatment decisions for occlusal surfaces. American Journal of Dentistry. February 2008, Volume 21, Issue 1, p. 25-29.
(34) Winn DM, Brunelle JA, Selwitz RH, et al. Coronal and root caries in the dentition of adults in the United States, 1988-1991. *Journal of Dental Research.* Feb 1996;75:642-651.
(35) Zandona AF and Zero DT. Diagnostic tools for early caries detection. *JADA.* 2006; 137:1675-84.
(36) Zantner, C., P. Martus and A.M. Kielbassa, Clinical monitoring of the effect of fluorides on long-existing white spot lesions. *Acta Odontologica Scandinavica*, 64 (2006), pp. 115–122.
(37) Zhang, L., Nelson, L.Y., and Seibel, E.J. (2011) Red shifted dental fluorescence in enamel and dentin, *Journal of Biomedical Optics* 16(7): 071411-1-5.

(38) Zhang, L., Nelson, L.Y., Berg, J.H., and Seibel, E.J. (accepted) Spectrally enhanced image resolution of tooth enamel surfaces. Lasers in Dentistry XVIII, Proc. SPIE vol. 8208.
(39) Meyer-Lueckel H, Paris S. Progression of artificial enamel lesions after infiltratin with experimental light curing resins. *Caries Res* 2008; 42:117-124.
(40) Gomez SS, Basili CP, Emilson CG. A 2-year clinical evaluation of sealed noncavitated approximal posterior carious lesions in adolescents. *Clin Oral Invest* 2005;9:239-243.
(41) Martignon S, Ekstrand KR, Ellwood R. Efficacy of sealing proximal early active lesions: an 18-month clinical study evaluated by conventional and subtraction radiography. *Caries Res* 2006;40:382-388.
(42) Martignon S, Ekstrand KR, Gomez J, Lara JS, Cortes A. Infiltrating/Sealing Proximal Caries Lesions: A 3-year Randomized Clinical Trial. *J Dent Res* 2012;91(3):288-292
(43) Paris S, Hopfenmueller W, Meyer-Lueckel H. Resin infiltration of caries lesions: an efficacy randomized trial. *J Dent Res* 2010;89:823-826
(44) Meyer-Lueckel H, Bitter K, Paris S. Ranodmized Controlled Clinical Trial on Proximal Caries Infiltration: Three-Year Follow-Up. *Caries Res* 2012;46:544-548
(45) Ekstrand KR, Bakhshandeh A, Martignon S. Treatment of proximal superficial caries lesions on primary molar teeth with resin infiltration and fluoride varnish versus fluoride varnish only: efficacy after 1 year. *Caries Res* 2010;44:41-46
(46) Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of parallel-group randomized trials. *Lancet* 2001;357:1191-1194.
(47) ISO (International Organization for Standardization), Clinical Investigation of medical devices for human subjects - #14155:2011, ISO Central Secretariat: Geneva, Switzerland
(48) EMEA (European Medicines Agency), Guideline for Good Clinical Practice, 2002, London, Great Britain
(49) Kidd E, Mejàre I, Nyvad B. Clinical and radiographic diagnosis. In: Fejerskov O, Kidd E. *Dental caries – The disease and its clinical management.* Copenhagen: Blackwell Munksgaard; 2003. p.111-128.
(50) Murray JJ, Majid ZA. The prevalence and progression of approximal caries in the deciduous dentition in British children. *Brit Dent J* 1978;145:161-164.
(51) Araújo FB, Araújo DR, Sanots CK, Souza MAL. Diagnosis of approximal caries in primary teeth: radiographic versus clinical examination using tooth separation. *Am J Dent* 1996;9:54-56
(52) Kidd E, Pitts NB. A reappraisal of the value of the bitewing radiograph in the diagnosis of posterior approximal caries. *Brit Dent J* 1990;169:195-200.
(53) Rimmer PA, Pitts NB. Temporary elective tooth separation as a diagnostic aid in general dental practice. *Br Dent J* 1990;169:87-92.
(54) American Academy of Pediatric Dentistry, Endorsement: Prescribing dental radiographs for infants, children, adolescent and person with special health care needs, in *2005-06 Oral Health Policies and Clinical Guidelines (AAPD)* 2005

Statistical Analysis Plan

NCT Number: **Clinical Trial Proximal Caries Infiltration and Detection**

NCT Number: NCT01796106

Sample Size Determination

The primary endpoint in this study is the proportion of study lesions that have progressed, whereby a difference in caries progression of 40% after 2 years between resin infiltrated teeth and control will be assumed. This difference is based on a previous infiltration study by Ekstrand et al. [45] who reported a 1-year difference in caries progression in primary teeth of 39% (resin infiltration (23%) vs. control (62%)), which was furthermore comparable to results obtained in young adults. Martignon et al [42] for example reported a difference in caries progression in permanent teeth of 37% and 38% after 1 and 2 years respectively; and Meyer-Lueckel et al. of 30% after 18 months.

Based on an assumed difference in caries progression of 40% between resin infiltrated teeth and control, with alfa = 0.05 and a power of 80% the calculated sample size (t-test; matched pairs) would be 42 lesions to find significant differences. To allow for a potentially attrition rate of at least 20% over a period of 2 years a total of 50 lesions will be included.

Statistical Analysis

All evaluations are performed by one trained examiner. The primary outcome is proportion of study lesions that progressed after 2 years as measured via dental examination and pairwise comparison of radiographs. Differences between groups will be tested using Fisher's exact test.

Secondary outcomes are the proportion of study lesions that progressed after 1 year as well as change in categorical lesion depth (progression to next depth category lesion; E1->E2->D1->D2->filling) after 1 and 2 years as measured by pairwise comparison of radiographs. In addition, the change in categorical lesion depth will be determined via SFE laser optical device imaging after 1 and 2 years and compared to the change in categorical lesion depth as measured by pairwise comparison of radiographs. Differences in categorical lesion depth will be analyzed with Chi-square tests with 95% confidence interval (95% CI) and P = .05.