

# **Decision Aids for the Management of Suspicious Occlusal Caries Lesions**

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## **STATEMENT OF COMPLIANCE**

The study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

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## SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and guidelines.

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The signature below constitutes:

- 1) acknowledgement of having read this protocol version (as indicated in the upper right corner of this page) and the attachments;
- 2) an assurance that this individual will conduct all of his or her assigned study tasks according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and guidelines; and
- 3) an assurance that this individual will read and follow all study plans applicable to his/her role on the study (e.g., Regional Coordinators will read and follow the Manual of Procedures, Practice Training Binder, Clinical Monitoring Plan, and other applicable plans developed in the future).

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## LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CC	Coordinating Center
CDM	Clinical Data Manager
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
Co-I	Co-Investigator
CRF	Case Report Form
DMP	Data Management Plan
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
GEE	Generalized Estimating Equations
GPI	Grant Principal Investigator
HIPAA	Health Insurance Portability and Accountability Act
HSPT	Human Subjects Protection Training
ICC	Intraclass correlation coefficient
IRB	Institutional Review Board
MOP	Manual of Procedures
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
NND	National Network Director
OHRP	Office for Human Research Protections
OC	Oracle Clinical
OCTOM	Office of Clinical Trial Operations and Management
pCRF	Paper Case Report Form
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RAS	Regional Administrative Sites
RC	Regional Coordinator
SAE	Serious Adverse Event/Serious Adverse Experience
SMS	Survey Management System



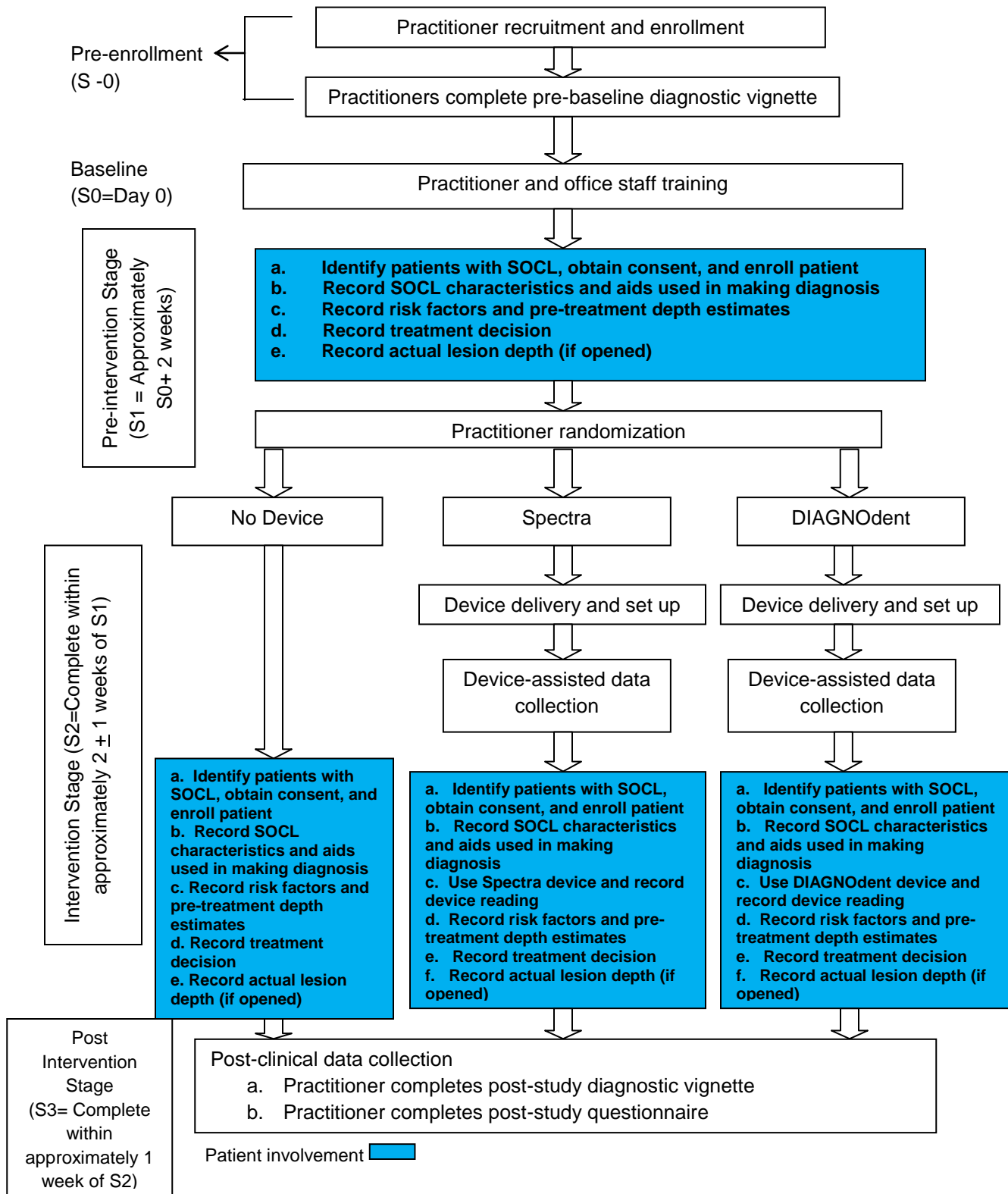
SOCL	Suspicious Occlusal Caries Lesions
SPI	Study Principal Investigator
UAB	University of Alabama at Birmingham
UP	Unanticipated Problem

## PROTOCOL SUMMARY

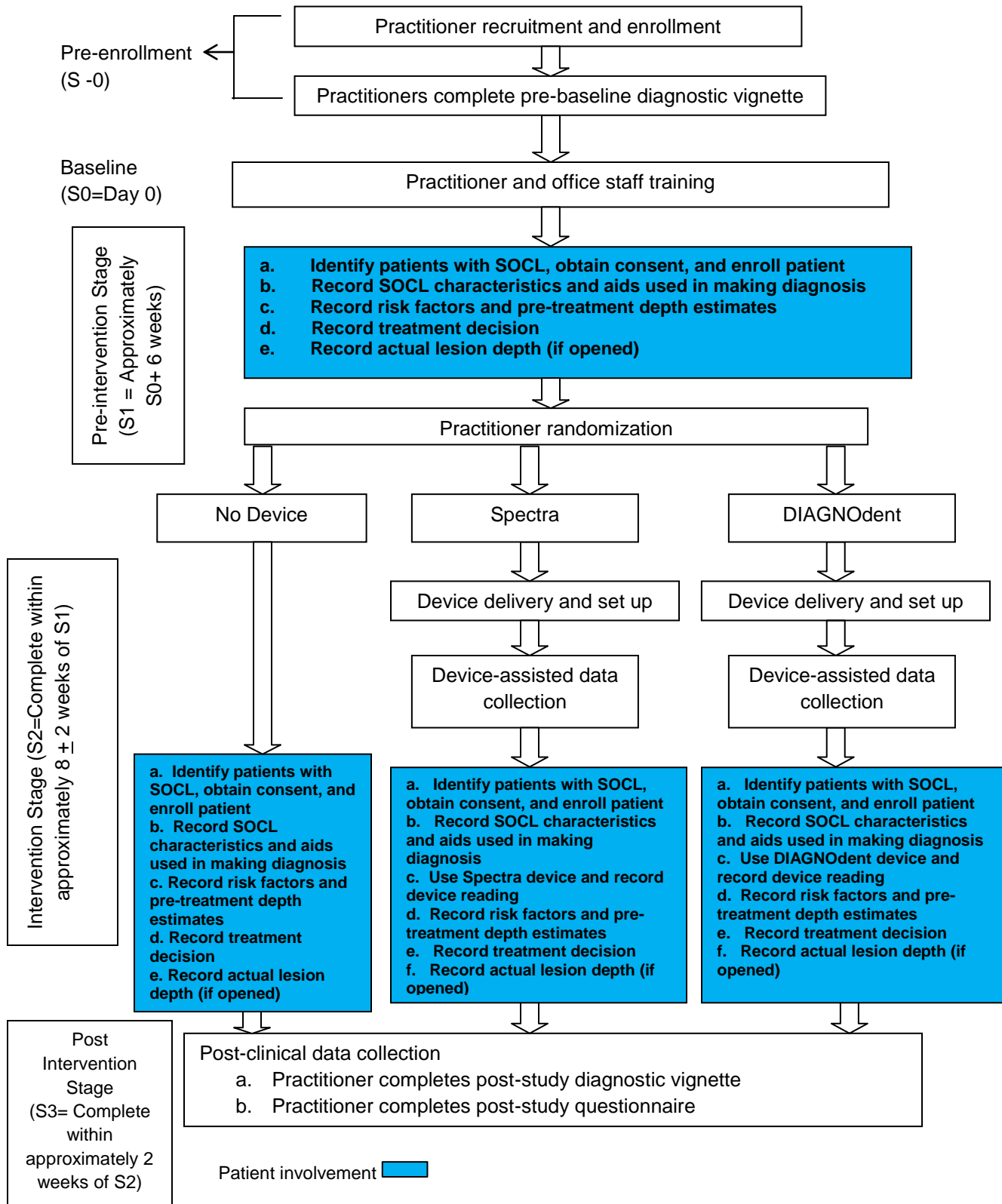
<b>Title:</b>	Decision Aids for the Management of Suspicious Occlusal Caries Lesions (SOCL)
<b>Précis:</b>	<p>This study examines the effect of the use of two diagnostic devices on dental practitioners' identification and treatment of SOCLs. The study will be conducted in two stages as 1) a pilot phase and 2) full study phase.</p> <p>During the pre-intervention period, practitioners will collect and record descriptive and treatment information for SOCLs they identify. Practitioners will then be randomized into one of 3 study arms: no diagnostic device, DIAGNOdent<sup>®</sup>, and Spectra<sup>®</sup>, and will collect and record similar information as the pre-intervention period enrolling SOCLs. They will also complete diagnostic vignettes at the beginning and end of the study, as well as a post-study questionnaire. Analyses will examine differences in proportion of SOCLs treated surgically in the groups with and without the diagnostic device; and, for those treated surgically, differences in the proportions of SOCLs with extension into dentin. Differences in pre- and post-study responses on the vignettes will suggest which components of the decision-making process involved in SOCL identification and management have been modified by use of the diagnostic devices.</p>
<b>Objectives:</b>	<p><b>Primary:</b> The primary objective is to quantify the difference in proportion of SOCLs treated operatively when a diagnostic device is used compared to when one is not used, and to quantify the difference in proportion of SOCLs treated operatively that extend into dentin when a diagnostic device is used compared to when one is not used.</p> <p><b>Secondary:</b> The secondary objectives are to identify the clinical characteristics of SOCLs that best predict caries that extends into dentin, to determine whether the principal factors used by participating practitioners in managing SOCLs change when a caries detection device is employed, and to obtain practitioners' assessments of the utility of the devices in their practices. Because the vignettes are designed to simulate the clinical situations for which data collection will occur, their fidelity in predicting practitioners' treatment decisions will also be assessed, providing a unique and needed insight into their utility for future studies of diagnostic decision-making.</p> <p>The overall goal of the study is to assess the contribution of these devices in dentists' decision-making processes surrounding SOCLs, an assessment that has not yet been attempted, despite the growing popularity of these devices.</p>
<b>Population:</b>	In this study, dental practitioners (n=108) are the primary subjects being studied, as the principal and secondary objectives address changes in their behaviors and the results of those changes. Patients, while also considered to be subjects, serve as stimuli for eliciting practitioner behaviors and assessing results of those behaviors.

	<p><b>Practitioners:</b> 108 practitioners will be recruited to participate in the proposed study overall including the pilot and full study phase. All six regions will participate in the proposed study. Six (6) practitioners will participate in the pilot phase and enroll 10 SOCLs each while 90 practitioners will participate in the full study phase and enroll 40 SOCLs each.</p> <p><b>Patients:</b> Patients (n=3660) with one or more SOCLs are eligible for enrollment. Patients under the age of 19 (this age may vary by state) will need to have the informed consent signed by the parent or legal guardian, as well as provide assent.</p>
<b>Number of Practitioners:</b>	Approximately 108 National Dental PBRN practitioners among the six regions of the network or approximately 18 per region
<b>Study Duration:</b>	Approximately 20 months
<b>Subject Participation Duration:</b>	<p><b>Practitioner:</b> Approximately 1-2 months for the pilot phase and 4-8 months in the full study (Practitioners will need to complete a pre-study vignette, undergo data collection training, participate in pre-intervention data collection, train on the use of the devices if randomized to the device arm, participate in the intervention phase data collection and complete a post-study vignette and post-study questionnaire)</p> <p><b>Patient:</b> Most patients will be seen for only one visit, some may require two visits depending on regularly scheduled treatment.</p>
<b>Estimated Time to Complete Enrollment:</b>	Within a practice, patient enrollment will occur in two blocks: pre-intervention phase lasting approximately one week in the pilot phase and four in the full study and the intervention phase lasting approximately two weeks in the pilot phase and eight weeks in the full study.

### Schematic of Study Design: Pilot Phase



### Schematic of Study Design: Full Study



## 1 KEY ROLES AND CONTACT INFORMATION

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## 2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

### 2.1 Background Information

A topic of interest mentioned numerous times among practitioners is the management of “questionable” or “suspicious” occlusal caries lesions (SOCL). SOCLs can be defined as occlusal surface areas where visual, tactile, and radiographic signs are insufficient to definitively diagnose caries but where some of these signs are present<sup>1</sup>. Although this problem is faced by many practitioners, there has been little careful clinical research and no evidence-based assessments regarding this common clinical problem<sup>1-2</sup>.

It is not clear what proportion of SOCLs are, in fact, active dentinal carious lesions. Only three studies have examined the issue, and their results do not resolve the question<sup>3-5</sup>. Clinical excision of lesions demonstrated that 51% had penetrated the dentin<sup>3</sup>, while histologic examinations found the percentages to be 41%<sup>4</sup>, and 44%<sup>5</sup>. Over a two-year observation period, one-half of the originally identified SOCLs were followed with no intervention, except when the lesion was deemed to have progressed to a definitive caries lesion with dentinal involvement. At the end of this two-year observation period, only 16% of the lesions that were followed were deemed to have progressed<sup>5</sup>. Additionally, a recent study on early occlusal lesions found that approximately  $\frac{1}{3}$  of lesions that were deemed to be in the dentin were rapidly progressing. This means that  $\frac{2}{3}$  of these lesions were slowly progressing (which could mean inactive or in the process of remineralizing)<sup>6</sup>. The results of these studies suggest that non-surgical intervention is the appropriate intervention for a majority of these lesions.

Not surprisingly, the lack of clarity regarding the presence and activity of dentinal caries associated with SOCLs leads to uncertainty among dentists over how to manage these lesions. Our own preliminary studies indicated that there is substantial variation among dentists in decisions regarding the application of preventive measures and also the use of surgical intervention to remove the suspicious tissue and place a restoration<sup>7</sup>.

Dentists' uncertainty about the management of SOCLs has been reflected in the introduction and rapid uptake of caries detection, or caries detection devices. Many dentists are turning to these devices in the hopes that they will provide more certainty, i.e., that they will accurately identify the SOCLs where caries is present and has penetrated into the dentin. The most recent systematic review of these devices, in 2013, concluded that there is only limited evidence supporting their use as adjuncts to clinical decision making<sup>8</sup>. A systematic review of the most popular of these devices found that its specificity in the detection of enamel lesions was low, meaning that many enamel lesions were incorrectly classified as penetrating the dentin,<sup>9</sup> and this problem of inadequate specificity leading to “false positives” and unnecessary surgical intervention has continued to concern those who evaluated its performance.<sup>10-12</sup>

All of the existing studies regarding the performance of these caries detection devices are limited to assessing their performance (sensitivity, specificity, ROC analyses) in highly organized clinical studies, both *in vitro*, and less often, *in vivo*. The actual outcomes of routine daily use of the devices by practicing dentists has never been explored. Thus, the extent to which use of a diagnostic device improves the accuracy with which dentists detect the presence of caries, and if present, its degree of penetration, is unknown. Further, the extent to

which the devices result in dentists making more appropriate management decisions is equally unclear.

## 2.2 Rationale

The overall significance of the study is in determining whether the use of caries detection devices increases congruence with current best evidence. Based on three studies done in the 2005-2012 cycle of the former Dental PBRN<sup>3,13-15</sup>, for many dentists the uncertainty leads to surgical treatment when it is possible that non-surgical treatment could effectively stop caries progression and at the same time spare tooth tissue.

The nation's network offers an excellent opportunity to conduct a study that evaluates the outcomes associated with the use of two of the most popular of the diagnostic devices. The study will determine whether dentists who use a device treat SOCLs surgically more often, with the same frequency, or less frequently, than dentists not relying on a device. The study will also determine -- among those SOCLs that are opened -- whether the proportion of lesions that extend into the dentin when dentists are using a device is more than, the same, or less than when no device is used.

Additionally, pre- and post-study diagnostic vignettes that simulate the decision making process will afford an understanding of what cues in the lesion presentation are influential in dentists' management decisions, and to what extent information provided by a diagnostic device reinforces or overrides those cues. Because the vignettes are designed to simulate the clinical situations for which data collection will occur, their fidelity in predicting practitioners' treatment decisions will also be assessed, providing a unique and needed insight into their utility for future studies of diagnostic decision-making. Finally, dentists' assessments of the utility of the devices in their practices will also be gained. The overall goal is to assess the contribution of these devices in dentists' decision-making processes surrounding SOCLs, an assessment that has not yet been attempted despite their growing popularity.

## 2.3 Potential Risks and Benefits

### 2.3.1 Potential Risks

**Practitioner:** There may be some initial disruption to practice routine to accommodate data collection procedures. As with any study, there is the possibility of breach of confidentiality. Appropriate precautions will be taken and procedures will be followed to maintain confidentiality.

**Patient:** As with any study, there is the possibility of breach of confidentiality. Appropriate precautions will be taken and procedures will be followed to maintain confidentiality. These include use of unique study codes for participants, encryption of data for transmission to the Coordinating Center (CC), and password-protected computers for data storage. Compliance with all Institutional Review Board (IRB) regulations concerning data collection, data analysis, data storage, and data destruction will be strictly observed.

The practitioner decides the treatment; risks of dental procedures provided as part of normal clinical care are not considered to be study-related.

Because the study requires that practitioners have not routinely used the devices in their practices, device use is a study-related variation from the normal diagnostic process that the participating dentist provides. However, the DIAGNOdent® and Spectra® devices are routinely

used in some dental practices. Dentists in the study will be trained in the proper use of the device and will follow all manufacturers' instructions related to safety.

### **2.3.2 Potential Benefits**

The practitioners will benefit from a better understanding of their treatment decisions, and how the use of caries detection devices affects these decisions, if at all. The indirect benefit to the patients may be the ultimate improvements in dental diagnosis in daily clinical practice.

**Practitioner:** Exposure to new technology (if in device arm).

**Patient:** Patients will receive no direct benefit from study participation.

### 3 OBJECTIVES

#### 3.1 Study Objectives

**Primary:** The primary objective is to quantify the difference in proportion of SOCLs treated operatively when a diagnostic device is used compared to when one is not used and to quantify the difference in proportion of SOCLs treated surgically that extend into dentin when a diagnostic device is used compared to when one is not used.

**Secondary:** The secondary objectives are to identify the clinical characteristics of SOCLs that best predict caries that extends into dentin, to determine whether the principal factors used by participating practitioners in managing SOCLs change when a caries detection device is employed, and to obtain practitioners' assessments of the utility of the devices in their practices. Because the vignettes are designed to simulate the clinical situations for which data collection will occur, their fidelity in predicting practitioners' treatment decisions will also be assessed, providing a unique and needed insight into their utility for future studies of diagnostic decision-making.

#### 3.2 Study Outcome Measures

##### 3.2.1 Primary Outcomes

There are two primary outcomes that will be compared between the device and no device groups:

1. Surgical treatment of the lesion (yes/no); and
2. For lesions treated surgically, extension into dentin (yes/no).

##### 3.2.2 Secondary Outcomes

To identify the clinical characteristics of SOCLs that best predict caries that extends into dentin, the following patient and tooth level characteristics will be assessed:

*Patient characteristics*

Demographics (gender, age, race, ethnicity, has dental insurance, education level)

*Objective measures assessed by practitioner either through clinical observation or patient report:* Heavy plaque, high cariogenic diet, inadequate saliva flow, infrequent recall intervals, fluoride prescription or application, caries risk level (low/elevated); pre-estimate of caries depth

*Tooth characteristics*

Tooth number, luster, color, roughness; aids in making diagnosis; other teeth with lesions/white spots, restorations in the last three years

To determine whether the principal factors used by participating practitioners in managing SOCLs change when a caries detection device is employed, the following variables will be assessed prior to and after using the device, if in a device arm: Data from the vignette portion of the study will examine individual dentist (idiographic) decision equations, as well as overall (nomothetic) equation for treatment decisions. Further, in an exploratory manner, demographic

characteristics of the dentists (age race, sex, and experience in practice) will be assessed with the above-mentioned variables.

To obtain practitioners' assessment of the utility of the caries detection devices in their practices, the post-study questionnaire will address:

- ease of learning to use the device;
- adequacy of instructional materials;
- ease of using the device in practice, perceived accuracy of the device; and
- perceived utility of the device.

## 4 STUDY DESIGN

The study combines elements of a pre-and post-control group design and a randomized clinical trial. To achieve a sample of 1200 lesions for each of the three arms in the full study, we wish to enroll a total of 90 practitioners (total from all six regions) in the study, each of whom will enroll approximately 40 SOCLs (one lesion/patient), 20 enrolled/completed lesions during the pre-intervention phase, and 20 enrolled/completed lesions during the intervention phase. Thus, the patients enrolled will be representative of the patients with such lesions in the practitioners' offices.

### Overview of Study Schedule

There will be a 4-8 month window for practitioner enrollment. When a practitioner has completed the study pre-enrollment requirements and the region has IRB approval s/he will be ready to begin the study. Following enrollment, as part of their study training, practitioners will be trained as follows:

1. Study Procedure Training: RCs will provide study procedure training, and practitioners will also receive a training manual which will serve as a reference and will highlight important information.
2. Standardization Training Pertaining to SOCLs: During the Study Procedure Training with the practitioner, the RC will provide photographs of teeth with SOCLs and review the clinical characteristics of SOCLs. The RC will answer any questions the practitioner might have about these characteristics. The photographs will be given to the practitioners to place in the operatory for review as needed.
3. Device Delivery and Set Up: Practitioners randomized to the device arm following the pre-intervention data collection phase will receive the devices from the RAS, and the RAS will assist with device set up.
4. Device Familiarization: Practitioners randomized to the device arm will familiarize themselves on device use, thus simulating as closely as possible what occurs in practice if dentists purchase devices on their own. Practitioners will "self-train" according to manufacturer's instructions and manufacturer-provided materials (e.g. DVD, Webinar). Practitioners may seek further guidance on device use from their colleagues and may query a manufacturer representative. Device Familiarization will also involve practitioners familiarizing themselves with the devices through unsupervised clinical use with patients. This device familiarization period is anticipated to take approximately four weeks for all practitioners randomized into the device arms.

Before beginning the clinical portion of the study, practitioners will complete pre-study vignettes that require practitioners to make diagnostic decisions with scenarios and photos. They will be asked how likely they would be to choose a specific treatment procedure. This vignette will be completed online. Following the vignette, all practitioners will participate in an approximate 4 week long pre-intervention period without the assistance of a caries detecting device and will enroll patients with at least one lesion. Practitioners will record data for one lesion per patient, which will be determined randomly. If more than one lesion is found in one patient, practitioners will choose the tooth that is closest to the day of the month on the day they are observing the patient. They will choose the tooth in an ascending order. For example, if the day of the month is the fourth, the practitioner will choose the higher number tooth closest to the fourth. Data to be recorded include pre-treatment

findings, a treatment decision, and if necessary, post-treatment findings. If, during the first two weeks of the pre-intervention period, practitioners are unable to enroll five patients with a SOCL, or do not wish to further participate in the study, they may be withdrawn and new practitioner(s) will take their place prior to randomization. The goal for enrollment is approximately 20 enrolled/completed patients each with one SOCL.

Following the pre-intervention period, practitioners will be randomized into one of three arms (Spectra<sup>®</sup>, DIAGNOdent<sup>®</sup>, and no device). Practitioner randomization will occur after the pre-intervention period.

Randomization assignments will be performed by the CC via the National Dental PBRN practitioner database. The RAS staff will notify the practitioners on their randomization assignment. Randomization assignments will be stratified by region; therefore, each region will receive the devices prior to the start of the study. Once the RAS staff receives notification of the practitioner's randomization assignment, the practitioner will receive the device (if assigned to arm) from the RAS.

Following device familiarization if randomized to a device arm, practitioners will participate in the intervention period. We anticipate the intervention period to take approximately eight weeks per practitioner to train on the devices and enroll/complete 20 patients each with one lesion. Our previous study had shown that practitioners, on average, enrolled 19 patients per month. Each patient's (subject's) participation will be limited to the duration of the dental visit. The patient will undergo further caries detection using a device if in a device arm, and data collection and recording procedures will be performed. Practitioners randomized to the no device arm will begin the intervention stage after having received their randomization assignments.

Following the intervention phase, practitioners will complete a post-study vignette with scenarios and clinical photos. This will be completed online. For those assigned to a device arm, practitioners will also complete a post-study questionnaire on how they "self-trained" on the device, resources utilized for device familiarization, and utility of the device. For those not assigned to a device arm, practitioners will complete a post-study questionnaire on the vignette and participation in the study.

### **Pilot Testing**

The Study Team will pilot test the study with up to six practitioners. The purpose of the pilot phase of the study is to identify possible issues with the study procedures and materials that might cause difficulty in implementation or compromise the quality of data that is collected. This phase is intended to provide an opportunity for practitioners to identify problems in the practical application of the study methods that were not anticipated during the study development. The primary outcome of the pilot study is the identification of any issue that may affect critical data elements of the study (see Appendix C of the Data Management Plan (DMP) for the list of critical data elements). If critical data elements are affected or changes are made to the design of the data collection forms, downtime after the pilot would be necessary to modify study documents and/or processes. If critical data elements are not affected, the full study launch will occur without downtime following the pilot.

Data collected in the pilot phase of the study will not be included in the full study dataset. If changes are made to procedures or materials, the two phases might not yield equivalent information. Even if no changes are required, the practitioners' knowledge that they are

participating in a pilot phase could lead to systematic differences relative to the main data. This could lead to reduced rather than increased study power if these data are combined.

The duration of the pilot phase is anticipated to be completed in approximately 1-2 months in that practitioners will enroll approximately 5 SOCLs each in the pre-intervention and intervention phase.



## 5 STUDY ENROLLMENT AND WITHDRAWAL

**Practitioner:** Practitioners may withdraw from the study before randomization and be replaced. After randomization, they will not be replaced.

For this study, the term “practitioner” will be limited to dentists only who are licensed in the US to treat patients on a recurring basis. Hygienists will not be included in this study due to the pre-and post-study vignettes which include clinical scenarios and operative decisions.

**Patient:** Patients under the age of 19 (this age may vary by state) will need to have the informed consent signed by the parent or legal guardian, as well as provide assent. Racial and ethnic minorities will be included in the study at least proportional to their composition in the dental community. Emancipated minors will be treated as adults, as allowed by regional IRBs.

### 5.1 Subject Inclusion Criteria

**Practitioner:** In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Is enrolled in the National Dental PBRN;
- Has completed an Enrollment Questionnaire;
- Is a general or pediatric dentist who is licensed in the United States to treat patients and treats patients in the United States on a recurring basis;
- Is trained and certified in Human Subjects Protection Training;
- Has attended or viewed a National Dental PBRN orientation session or attended at least one annual regional meeting of practitioners or has attended a National Dental PBRN workshop at IADR or AADR.
- Performs restorative dentistry routinely in their practices as reported on the enrollment questionnaire;
- Has no clinical experience (no history of routine use in practice within the past one year) with either of the devices being used in the study and declares no conflict of interest with the corporations that produce DIAGNOdent<sup>®</sup> and Spectra<sup>®</sup>; and
- Is able to complete the pre-and post-study vignettes online.

**Practice:** If a practitioner is in a practice where they share an operatory (including a hygiene chair) only 1 dentist can be recruited from that practice.

**Patient:** In order to be eligible to participate in this study, an individual with a SOCL must meet all of the following criteria:

- Willing to provide consent according to regionally approved procedures and/or obtain parent/legal guardian permission as applicable;
- Willing to comply with all study procedures;

- Is six years of age or older; and
- Has not participated in the study previously. (Patients will be enrolled only once throughout the study (this includes the pre-intervention and intervention phases for the pilot study and full study).

**Tooth:** In order to be eligible to be included in this study, a tooth with a SOCL must meet all of the following criteria:

- Permanent tooth;
- No radiographic evidence of caries into dentin based on available radiographs;
- Caries into dentin is suspected due to roughness, surface opacities, or staining;
- No symptoms of sensitivity to sweets, cold, air, etc.;
- No restoration on the occlusal surface; and
- No sealant on occlusal surface.

## 5.2 Strategies for Recruitment and Retention

**Practitioner:** Practitioners will be recruited based on the inclusion criteria stated above. They will submit their logs and example CRFs to the RCs (according to regionally approved secure data handling procedures) on a weekly basis to ensure their compliance with the study requirements.

We will need 90 practitioners to participate, or approximately 15 per region for the full study. Each region will recruit two additional practitioners who will serve as back-up participants for the study if a practitioner drops out prior to randomization. These back-up practitioners will complete in-office training, the pre-study vignette, and the pre intervention phase of the study. An additional six practitioners or approximately one per region will be recruited for the pilot phase of the study. Thus the overall number of practitioners in the study will be 108.

Practitioners who meet eligibility criteria will be surveyed for interest in participating in the study. We will rely on the RCs from the six RASs to help recruit practitioners into the study. RCs are 'the face of the nation's network', and many have strong, positive relationships with network members. Practitioners will be compensated for the time required to do the research, receiving \$50 for the pre-study vignette, \$25 for completing the patient assessment CRFs for each patient s/he enrolls, \$50 for the post-study vignette, and \$25 for the post-study questionnaire (both device and no device arms).

**Patient:** This study requires no post-treatment follow-up, and hence retention of patients is not needed. Patients will be recruited by the practitioner when they are seen in the office and are diagnosed with a SOCL. Designated office personnel will introduce the study to patients who meet inclusion criteria when they are seen for a dental appointment. For patients who express interest in participating in the study, a designated individual will execute regionally approved consent procedures with the patient. It is presumed that these patient recruitment tasks will be consolidated to one or two office personnel. However, each office should have the latitude to designate tasks that will work best within the normal operating procedures for their practice. Enrolled subjects will not receive any compensation for their participation in the study.

### 5.3 Subject Withdrawal

**Practitioners:** As part of the study Quality Assurance (QA) program practitioners will be asked to submit their logs and examples of completed CRFs on a weekly basis. Practitioners will be monitored regularly to ensure they adhere to the protocol. Practitioners may withdraw from the study at any time or be withdrawn from the study during the pre-intervention stage if they are unable to enroll at least five patients who present with a SOCL during the first two weeks.

**Patients:** Subjects may withdraw voluntarily from the study.

#### 5.3.1 *Reasons for Withdrawal*

**Practitioner:** Practitioners may choose to withdraw from the study if they are unable or unwilling to adhere to the protocol.

**Patient:** Subjects are free to withdraw from participation in the study at any time upon request. Since most patients will be seen for one visit, it will be rare for a patient to withdraw from the study.

An investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE) or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

#### 5.3.2 *Handling of Subject Withdrawals*

**Practitioner:** If a practitioner withdraws from the study prior to randomization, he/she will be replaced by another practitioner. If the practitioner withdraws from the study after randomization, he/she will not be replaced.

**Patient:** We expect the withdrawals will be extremely infrequent. If a patient withdraws due to an unanticipated event, we will follow-up to determine if it constitutes an unanticipated problem.

### 5.4 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for suspension or termination.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects;
- Insufficient adherence to protocol requirements;
- Data that are not sufficiently complete and/or evaluable; and
- Determination of futility.

## 6 STUDY SCHEDULE

Those National Dental PBRN dentist practitioners who opt to participate will be sent information and instructions pertaining to the study. These instructions will provide information for the dentist(s) and staff who will help to execute the study. A detailed Practice Training Binder will be provided to each practice in written form prior to initiation of the study in the practice. The Practice Training Manual will carefully describe the subject selection procedures, methods for approaching subjects and obtaining informed consent (according to regional approvals), methods for data collection, and other study procedures. A summary flow chart will be sent to the practices with a description the study visit and an overview flow chart of the study. This will provide a simple, single page reference for office personnel involved in the study. In addition, in-person meetings (or teleconferences) with office staff will be held to provide further instruction in completing CRFs. The RC will also meet (or have an individual telephone call) with the participating practitioners prior to initiating the study to make sure that they and their office staff understand the study procedures.

The study will proceed in stages: 1) each region will enroll practitioners into the study who have completed IRB-mandated training; 2) practice personnel receive necessary IRB training and mail or in-person visits to have them sign practitioner informed consent forms (if required by that region's IRB), UAB Master Service Agreement, and similar documents; 3) RCs will ensure practices are trained in the appropriate study procedures (see below); 4) practices enroll subjects into the study. The CC along with the RAS and RCs will coordinate the launch of the study. Once the RC has trained an office in the practice procedures, that practice should begin recruiting subjects into the study immediately, or as soon as possible.

An overview of study procedures to be completed at each study visit can be found in Appendix A.

### 6.1 Practitioner:

#### 6.1.1 *Pre-Enrollment (S -0)*

Activity 1: Practitioner completes pre-intervention diagnostic vignette

#### 6.1.2 *Enrollment/Baseline (S0= Day 0)*

Activity 2: Practitioner and office staff training

#### 6.1.3 *Pre-intervention Stage (S1)*

***(Pilot Phase: Complete within approximately 2 weeks following S0***

***Full study: Complete within approximately 6 weeks following S0)***

Activity 3: Pre-intervention patient data collection procedures lasting approximately one week in the pilot phase and four weeks in the full study (see Section 6.2 below)

Activity 4: Practitioner is randomized into one of three arms (no device, DIAGNOdent, Spectra).

#### **6.1.4 Intervention Stage (S2)**

***(Pilot Phase: Complete within approximately 2 weeks  $\pm$  1 week following S1 Completion)***

***Full Study: Complete within approximately 8  $\pm$  2 weeks of S1 Completion)***

Activity 5: If the practitioner is randomized to the device arm, then he or she will undergo device familiarization. The device familiarization will include practitioners viewing the manufacturer's instructions and familiarizing themselves with the devices through unsupervised clinical use with patients prior to using the device for study data collection.

Activity 6: Patient data collection procedures (see Section 6.2 below)

#### **6.1.5 Post-Intervention Stage (S3)**

***(Pilot Phase: Complete within approximately 1 week following S2 Completion)***

***Full Study: Complete within approximately 2 weeks of S2 Completion)***

Activity 7: Practitioner completes the post-study vignette; and

Activity 8: Practitioner completes the post-study questionnaire

### **6.2 Patient:**

#### **6.2.1 Screening**

A potential subject may be recruited at any dental visit, not just examination or recall visits. During the course of a dental visit, when it is determined that a patient has an SOCL (using their usual methods for determination) and may be eligible for study participation, the designated office personnel will introduce the study to the patient and will ascertain that inclusion criteria are met. Enrollment, examination, and treatment may occur during the same dental visit at which eligibility was confirmed.

#### **6.2.2 Pre-intervention Stage Enrollment/Pre-Intervention**

For patients who express interest in participating in the study, a designated office individual will execute the consent process with the patient and ensure that the consent document has been executed. It is anticipated that in most cases this will be the dentist.

Screening Failures: If the patient expresses a verbal refusal to participate, this will be noted in a CRF/log; in such cases, the informed consent process will not be followed and the patient will be treated as a failure to provide consent. If the patient does not express a negative disposition to participation, the informed consent process will be carried out.

- Verify inclusion criteria;
- Obtain and document consent from potential participant;
- Practitioner record results of dental examination; and
- Practitioner record results of dental treatment.

#### **6.2.3 Intervention Stage Enrollment/Baseline**

- Verify inclusion criteria;
- Obtain and document consent from potential participant;

- Practitioner records results of dental examination, during which the device will be used (if in the device arm); and
- Practitioner records results of dental treatment.

## 7 STUDY PROCEDURES/EVALUATIONS

### 7.1 Study Procedures/Evaluations

**Practitioner:** The practitioner will complete a pre-study vignette online. After the study is complete, he/she will also complete a post-study vignette and questionnaire. For the pre-and post-study vignettes, practitioners will be given scenarios with photos. They will be asked to indicate how likely they would be to recommend a variety of treatments based on four cues: color, luster, and roughness of the lesion and caries risk characterization.

**Patient:** Once a patient has consented to participate and is enrolled, assessments are performed for the study based upon clinical examination findings and recorded on data collection forms. The forms will require the following information:

#### Provided by patient

- Subject age, sex, race, and ethnicity

#### Provided by practitioner

- Subject caries risk information;
- Clinical description of the lesion;
- Description of treatment provided;
- Clinical description of opened lesion, if operative intervention undertaken; and
- Practitioner's assessment of patients' caries risk category

### 7.2 Questionnaire Administration

**Practitioner:** Practitioners will be directed to a secure website to complete the pre-and post-study vignettes. After providing consent, practitioners will observe 16 unique patient profiles consisting of a text vignette and photo of a SOCL. The 16 profiles have been shown to be a valid and reliable approach to examining how practitioners use patient demographic cues to make lesion management decisions. For each patient profile, practitioners read a clinical vignette that describes the patient as having 4 various cues (color, luster, roughness of the lesion and caries risk characterization).

All practitioners will complete a post study questionnaire. This will also be done electronically similar to the vignettes. Practitioners randomized to the device arm will complete a post-study questionnaire on the utility and value of their device in addition to the pre-and post-study vignettes while practitioners on the no device arm will complete a post-study questionnaire on the vignette and participation in the study.

**Patient:** The patient will complete the demographics form.

## **8 ASSESSMENT OF SAFETY**

### **8.1 Specification of Safety Parameters**

Safety monitoring for this study will focus on unanticipated problems involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event.

#### **8.1.1 *Unanticipated Problems***

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

#### **8.1.2 *Serious Adverse Events***

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.



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## 8.2 Reporting Procedures

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB and to NIDCR within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to NIDCR within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR's centralized reporting system via Rho Product Safety:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: [rho\\_productsafety@rhoworld.com](mailto:rho_productsafety@rhoworld.com)

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

## **9 STUDY OVERSIGHT**

In addition to the GPI's and Study Principal Investigator's (SPI) responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of members with expertise in dentistry, practice-based research, study design and statistics. The DSMB will meet at least annually to assess safety and efficacy data for the study. If safety concerns arise, more frequent meetings may be held. The DSMB will operate under the rules of an NIDCR-approved charter that will be approved at the organizational meeting of the DSMB. At this time, most data elements that the DSMB needs to assess will be clearly defined. The DSMB will provide recommendations to the NIDCR.

## **10 CLINICAL SITE MONITORING**

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. The network RAS will be responsible for clinical site monitoring for this study. RCs at each RAS will provide study training to practitioner sites and perform clinical site monitoring activities, to evaluate study processes and documentation based on NIDCR standards and principles of Good Clinical Practice guidelines. Clinical site monitoring will not occur for the pre and post study vignette data collection study since the CC is responsible for launching the vignettes and collecting data received as part of the vignette.

All details about clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by Westat, under the direction of the National Dental PBRN, in collaboration with the NIDCR Office of Clinical Trials Operations and Management (OCTOM) and the NIDCR Program Official. The CMP will specify site training activities, the type and frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at each practitioner site. The RCs will provide reports of the findings from monitoring and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the practitioner, GPI, SPI, OCTOM, and NIDCR. NIDCR reserves the right to conduct independent audits as necessary.

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## 11 STATISTICAL CONSIDERATIONS

### 11.1 Study Hypotheses

The primary objective of the study is to quantify the difference in proportions of SOCL that are treated operatively among the study groups. The null hypothesis for this objective is that the proportions of SOCL that are treated operatively are not different among the three study groups. The corresponding alternative hypothesis is that the proportion of SOCL treated operatively differs among the groups. The main interest is in comparing the proportions of SOCL treated operatively between each of the device groups and the no-device group. The null hypothesis that will be tested for each of these comparisons is that the proportions of SOCL treated operatively does not differ between the groups versus the alternative hypothesis that the proportions differ. The study will also quantify the differences in proportions of SOCL that extend into dentin, among those that are treated operatively in each study group. The null hypothesis is that there is no difference among the groups in the proportion of operatively treated SOCL that extend into dentin. The alternative hypothesis is that the proportions of operatively treated SOCL that extend into dentin differ among the groups. Here again, there is particular interest in the two pre-planned comparisons between each of the device groups and the no-device group. The null hypothesis for each of these comparisons is that there is no difference in the proportions of SOCLs that extend into dentin between the device and no-device groups, and the alternative hypothesis is that there is a difference in the proportions.

A secondary objective of the study is to identify clinical characteristics of operatively-treated SOCLs that predict caries extending into dentin. For each of the clinical characteristics that is considered, the null hypothesis is that there is no association with extension into dentin and the alternative hypothesis is that there is an association with extension into dentin. Practically, the goal will be to identify a multivariable statistical model that is predictive of caries extending into dentin. In addition to separate tests for each characteristic, the null hypothesis for the predictive model is that the set of clinical characteristics included in the model jointly have no association with caries extension into dentin. The alternative hypothesis is that a joint association is present.

### 11.2 Sample Size Considerations

Power to detect differences between each of the device groups and the no-device group was approximated based on two-sided testing with the Chi-square statistic, with adjustments for multiple comparisons and for the effect of clustering within practitioner. A Bonferroni-type adjustment was used to account for two comparisons: no device versus each of the device groups. This approach yields somewhat conservative estimates of power, since the two device-versus-control comparisons are pre-planned, and will each be conducted at the 95% confidence level in the statistical analysis of the actual study data, as described in the following section.

The unit of randomization is the individual practitioner. The effect of cluster randomization was taken into account in the calculation of study power and sample size requirements by adjusting the total sample size using the design effect, calculated as  $1 + (m - 1)\rho$ , where  $m$  = the average number of lesions per practitioner and  $\rho$  = the intraclass correlation coefficient (ICC). The effective sample size was calculated by dividing the total sample size by the design effect. The effective sample size is the number of observations which would be required to achieve the same power, using an independently-randomized design, as the cluster-randomized design with the given total sample size. Power and detectable difference estimates were then calculated for the chi-square statistic using the effective sample sizes for values of ICC from 0.0 to 0.05.

Two outcomes are of interest: the proportion of all SOCL that are opened and the proportion of opened SOCL that are carious. Practitioners will each contribute 20 lesions to the study during the intervention period. The planned recruitment of 30 practitioners per group yields a total sample size of 600 lesions per group for the first outcome. The total sample size for the second outcome will be the number of lesions that are opened. Because the study design does not include follow-up of individual patients, patient-level dropout is not anticipated to be a major consideration. Drop-out of practitioners is possible, and could cause the loss of multiple observations, depending on the number of patients that are accrued prior to the practitioner drop-out, up to a maximum of 30. Part of the intent of the pre-intervention run-in period is to identify practitioners who are not likely to succeed in recruiting the required number of patients, and to provide an opportunity for practitioners to drop out prior to randomization, so that they can be replaced without interference to the randomization process. Still, it is possible that practitioners might drop out after randomization. Anticipating a severe situation in which 10% of the initial 30 practitioners in each group drop out prior to contributing any data, power and detectable difference calculations were repeated for 27 practitioners per group, and a total sample size of 540 lesions per group. While this is an extreme and unlikely occurrence, the additional tables provide an indication of the effect of a substantial loss of data.

The expected rates of lesion opening are 50% for no device and 30-35% for the device groups. Differences in rates of opening that would be detectable with 80% power are as follows:

Difference detectable with 80% power	ICC					
	0.00	0.01	0.02	0.03	0.04	0.05
Effective sample/group:	600	504	435	382	341	308
Detectable difference (%):	9.1	9.9	10.7	11.4	12.0	12.7
Rate in device group (%):	40.8	40.1	39.3	38.6	38.0	37.3

Assuming loss of 10% of practitioners per group, without contributing any data to the study:

Difference detectable with 80% power	ICC					
	0	0.01	0.02	0.03	0.04	0.05
Effective sample/group:	540	454	391	344	307	277
Detectable difference (%):	9.6	10.4	11.3	12.0	12.7	13.4
Rate in device group (%):	40.4	39.6	38.7	38.0	37.3	36.6

The proposed sample size would provide approximately 92% power to detect a difference in rates of opening of lesions, assuming the most restrictive set of conditions considered (rates of 50% vs 35%, ICC = 0.05). Power remains above 80% even if 10% of practitioners contribute no data. This provides some assurance that adequate power would be available, even if a somewhat smaller difference and/or somewhat larger value of ICC is observed.

The sample size for comparison of rates of caries into dentin among opened lesions will depend on the numbers of lesions that the dentists choose to open, and this will likely differ among groups. Assuming that 30 practitioners are recruited per group, each contributing 20 lesions, that 50% of lesions in the no-device group and 35% of lesions in the device groups will be opened, then the sample sizes for this question will be 300 lesions for the no-device group and 210 lesions in the device group. Assuming that 50% of opened lesions in the no-device group will be carious, the following table presents power to detect a difference between groups for percentages of 60%, 65%, 70% and 75% of opened lesions in the device group being carious.

	ICC					
	0.00	0.01	0.02	0.03	0.04	0.05
% caries in device group	Power (%)					
65%	87	80	73	67	61	56
70%	99	97	95	92	88	84
75%	99	99	99	99	98	97

Assuming loss of 10% of practitioners per group, without contributing any data to the study:

	ICC					
	0.00	0.01	0.02	0.03	0.04	0.05
% caries in device group	Power (%)					
0.65	83	75	68	62	56	51
0.7	98	95	92	88	84	80
0.75	99	99	99	98	97	95

### 11.3 Final Analysis Plan

This is the planned analysis based on the data we plan to collect. An appropriate statistical model must take into account both the level of measurement of the outcome variables and the study design. Both of the primary outcome variables, surgical treatment of the lesion and extension into dentin, may be appropriately represented as dichotomous variables. Each practitioner will be randomized to use a single device, or no device and no a priori study design levels defined within the level of practitioner. This approach yields a two-level hierarchical study design. A characteristic of this two-level model is the presence of correlation among the multiple observations obtained from each practitioner. The primary analysis framework will be based on mixed-model logistic regression analysis, implemented with generalized estimating equations (GEE), accounting for correlation among the clusters of observations made by the same practitioners. These models will include a term representing the individual practitioner as a random effect and study arm as a fixed effect. Additional control variables, including region, may be included if it is found that these are needed to account for possibly different distributions of practitioner or patient characteristics. Details of the analysis approach and related considerations are provided in Appendix E

Initial exploratory analyses will be conducted for the entire study data set, in order to characterize the empirical distributions of each variable, to identify possible errors in the data, and to evaluate the proportion of missing values. Descriptive analyses will also be conducted to evaluate possible associations of practitioner and patient characteristics with outcome measures or other study variables. Depending on the specific structures of these auxiliary analyses, appropriate analysis models may include hierarchical methods, or single-level approaches such as contingency table analysis using the Chi-square statistic or ordinary analysis of variance or logistic regression analyses. Additional exploratory statistical analyses will be conducted to examine changes in practitioners' rates of operative treatment of lesions during the pre-randomization run-in period versus their rates during the post-randomization intervention period. Further analyses will be conducted to evaluate possible associations between pre- to post-randomization changes in practitioners' rates of operative treatment and variables representing practitioners' perception of changes in the decision-making process.

For evaluation of differences in proportions of lesions treated operatively among the intervention groups, the analysis data set will include all SOCLs that are enrolled by the study practitioners. The outcome variable for this analysis will be a dichotomous variable indicating whether the SOCL was treated operatively.

For the comparison of proportions of lesions treated operatively that have caries extending into dentin, the analysis data set will include all SOCLs that were treated operatively by the study practitioners. The outcome variable will be a dichotomous variable indicating whether the lesion extended into the dentin.

To determine whether the principal factors used by participating practitioners in managing SOCLs change when a caries detection device is employed, the Lens model analytic approach will allow for the determination of the unique contribution of each of the 4 principal features (color, luster, roughness, risk) to the treatment decision. An overall significance of each equation and the variance it accounted for will be determined for the decision to surgically intervene and the confidence of that decision. These represent the main a priori hypotheses from the decision study (vignette) portion of the project. In addition to those a priori hypothesized analyses, a number of more exploratory analyses are possible within the Lens model approach. This could include demographic characteristics of the dentists (age race, sex, experience in practice etc.). These individual difference variables would be included in the nomothetic analyses only. Finally, the similarity of treatment predictors will be examined across the in vivo and vignette portions of the study as an initial cross validation of the two approaches. We will examine the concordance rates and/or correlations between number of decisions to intervene across the two portions of the study and across groups (device trained vs. no device).

The proposed sample size, developed in the previous section was developed using conservative assumptions regarding effect size and potentially missing data. The study is anticipated to provide adequate statistical power even if approximately 20% of observations have missing values for some variables, depending on the differences and level of ICC that are actually observed in the study. Issues regarding missing values are presented in further detail in the Appendix E.

## **12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS**

Each participating site will maintain appropriate dental/medical and research records for this study, using the principles of good clinical practice and complying with regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

The following clinical records will be considered source documents where they are used to complete CRFs: clinical and office charts, memoranda and recorded data from automated instruments.

The following CRFs or portions of CRFs will be considered source documents, as it is not expected that all patients' clinical charts would contain the exact information collected on these CRFs: study tooth characteristics, patient risk factors, treatment plan; questions on ethnicity, race, and highest level of education from the Patient Demographics CRF.

All study source documents must be maintained in a secure manner, and practice personnel and network personnel will have access to source documents. Study source documents may include clinical records and as such are subject to HIPAA regulations. These records will be subject to examination and copying as stated elsewhere in this section.

The CC will use a survey management system (SMS) to program the online vignette. Practitioners will be sent an email invitation with a direct link to the online vignette. After a participant submits the data it will be available in the SMS. Only study personnel i.e. the study team, National Network Director (NND) and CC staff will have access to these data elements. All research computers and associated study documents will be password-protected.



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### **13 QUALITY CONTROL AND QUALITY ASSURANCE**

For the Quality Assurance (QA)/Quality Control (QC) activities associated with data collection and processing, the CC will develop a Data Management Plan (DMP) in which the specific data QA/QC procedures will be provided and a Quality Management section in the MOP to further detail the QA/QC process. In the DMP, the procedures will include the development of automatic data quality checks in the database system and the processes related to the data manual review, discrepancy management, delinquent data handling, data updates, data verification and approval, and database audit. A work instruction will be provided to the RCs at the RAS with the specified tasks, timelines of completing the tasks, roles and responsibilities.

The MOP will detail a QA/QC process associated with data collection on pCRFs that will include quality checks at the participating practices, followed by QA/QC review at the RAS prior to and after data entry into the web system. Data entered into the system will be compared against pCRFs. The RAS staff will ensure that discrepancies generated by the system are resolved in a timely fashion based on study requirements. The RAS staff will work with practitioners to clarify any data issues and maintain a tracking log for the data changes. The Data Manager at the CC will work with the RCs to ensure that all procedures are followed and that the data are checked according to the validation requirements specified from the study protocol. At the end of the study, the RCs will ensure that all data collected by the regional offices are entered and cleaned. The Data Manager at the CC will verify the completion of data entry and clarifications by running monitoring reports. Once confirmed that the data entry are complete and the data are verified and approved for accuracy, the database will be locked for final analysis. During the study period, when interim data analysis is needed, the Data Manager will coordinate the activities with the RCs and the Statistician. The interim datasets will be provided with the data collected as of the specified date. The data in those datasets will be cleaned if possible but may contain pending issues which will be provided to the Statistician if requested. The datasets will be provided to the Statistician via secure data transfer method. The Quality Management plan is detailed in Appendix B.

For the QA/QC activities associated with vignette data collection, procedures will include the development of automatic data quality checks and the processes related to the data manual review, discrepancy management, delinquent data handling, data updates, data verification and data audits. The SPI will work closely with the CC to ensure that the electronic data are being collected appropriately and confidentially.

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## **14 ETHICS/PROTECTION OF HUMAN SUBJECTS**

### **14.1 Ethical Standard**

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46.

### **14.2 Institutional Review Board**

It is recognized that this protocol must receive the approval of eight or more different IRBs, and each may have different criteria for subject informed consent. Therefore, different regions may have slightly varied informed consent procedures. For the purposes of this minimal risk study, any of the following will be considered acceptable by the study investigators, at the discretion of the responsible IRB: verbal consent; written consent; written information sheet provided prior to or at the time of data collection; written consent and authorization.

The protocol, consent form(s), recruitment materials and all participant materials will be submitted to the IRB for review and approval by each RAS. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

### **14.3 Informed Consent Process**

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

Patients enrolled as participants in this study must be six years of age and older, and must be able to provide either assent or consent, following local requirements for documenting consent for research participation. Patients under the age of 19 (this age may vary by state) will need to have the consent by the parent or legal guardian and must assent to participation. By regulatory definition, children are “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted”. In the United States the legal age of adulthood is a matter of state and local law. This means that who is legally considered a child may vary from state to state; in a large majority of states 18 years of age is the legal age of adulthood, but this is not true in every state, locality, or territory. State law also may address specific circumstances in which a

person younger than the age of adulthood is legally authorized to consent to medical procedures: for example, some states allow children younger than the legal age of adulthood to consent to the provision of contraceptive services. Certain states provide a mechanism for the emancipation of minors, through which a child younger than the legal age of adulthood may gain certain civil rights, which might include the legal ability to consent to research participation.<sup>16</sup>

The consent process will be documented in the clinical or research record.

Participating practices will designate who will execute informed consent for the study. In most cases this will be the practitioner(s). Any personnel who will be assigned to obtain consent will be defined as study personnel and will complete required IRB training. Consent will be obtained in the practice prior to enrolling a subject into the study.

#### **14.4 Exclusion of Women, Minorities, and Children (Special Populations)**

Racial and ethnic minorities will be included in the study at least proportional to their composition in the dentist's patient population. Individuals of any gender or racial/ethnic group may participate.

#### **14.5 Participant Confidentiality**

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Subjects will be assigned a unique identification number, which will be used to maintain study records and organize data transcripts. A file linking subjects' names with their unique identification number will be kept in a password-protected file on the CC's and RAS' computer.

The study monitor and other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, dental records for the study participants. The clinical study site will permit access to such records.

#### **14.6 Future Use of Stored Specimens and Other Identifiable Data**

There will be no specimens collected for this study. There will be a barcode for the data collection form for each patient enrolled. Forms will be kept in a locked office at all times. They will be stored for three years from the conclusion of the study.

## **15 DATA HANDLING AND RECORD KEEPING**

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate CRFs, and source documentation. The DMP is detailed in Appendix C.

Only study personnel (i.e., GPI, SPI, Co-I's, RCs, CC personnel) and clinical site monitors will have access to the study data elements in the study database as described in Section 15.3 Types of Data. Study personnel will include those who are on the approved IRB study protocol. All study personnel will have completed the required training elements for human subjects research certification.

### **15.1 Data Management Responsibilities**

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems must be reviewed by the investigator or designee.

Staff at the RAS will collect paper CRFs (pCRF) from practitioners and will enter data into the web system. For the pCRFs that are to be used as source documents (see Section 12), the RAS staff will ensure the forms are completed and the copies are maintained at practitioners' or regional sites. The RAS staff will ensure the data are entered and the discrepancies generated by the system are resolved in a timely fashion based on study requirements. The RAS staff will work with practitioners to clarify any data issues and maintain a tracking log for the data changes. To aid the data collection and data entry activities, the CC will provide pCRF completion and electronic data entry guidelines. Some or all of the pCRFs may also be sent to the CC for data entry by CC staff.

All data reported in the SMS will be checked by the CC staff for completeness and consistency. Any data issues identified will be communicated with the study team as appropriate according to the procedures specified in the DMP.

### **15.2 Data Capture Methods**

Patient data will be collected via pCRFs. The post-study questionnaire, pre- and post-study vignettes will be completed electronically via the SMS. The practitioners will be given either a link to the questionnaire and vignettes and/or a unique code in order to complete the questionnaire and vignette.

Study-specific pCRFs will be developed to include fields for all data elements required for practitioner and patient assessments. A Web-based data collection system will ensure that all required data are collected in the study database. Data fields in the database will be programmed to allow only certain values and ranges so that data entered from the web system can be validated and data errors be corrected. Reports and tools will be developed to help monitor the visit and data activities. The reports with the summary of the data completion by participants will be made available on the network web site.

After the paper data collection has been completed for a participant, the study materials for the participant may be placed in the participant's research file. The participant log will be consulted

to obtain the name of the patient corresponding to the study ID number printed on the CRF so that the dentist can cross-check information on the study form with the patient's dental chart. Questions about the data will be resolved by conferring with the staff member(s) who completed the CRF.

For the online post study questionnaire and vignettes the SMS will ensure that all required data are collected per protocol requirements, and the data fields in the system are checked for completeness and consistency so that data entered into the web system can be validated and data errors be corrected. Edit checks will be programmed into the web survey to correct data issues in real time. Reports or tools will be developed to help monitor the data activities. The reports with the summary of the data completion by the participants will be made available on the network web site if requested.

### **15.3 Types of Data**

Data that will be collected include responses from the pre- and post-study vignettes that will be completed by the practitioner. Responses from the patient data collection form will include demographic, lesion characteristics, and caries assessments.

### **15.4 Schedule and Content of Reports**

Reports to monitor enrollment will be produced every two weeks during the participant enrollment period, until enrollment targets are attained and enrollment is closed. These reports will contain a section for accrual information in aggregate and will also contain separate sections for each region, with information regarding participant accrual by site.

Reports to the DSMB will be produced at least annually, and may be produced more frequently at the request of the DSMB. As noted in Section 9 Study Oversight, most data elements for inclusion in the DSMB reports will be clearly defined at the organizational meeting of the DSMB.

Study progress and interim analysis reports that address objectives will be produced at the discretion of the CC Statistician, in consultation with the SPI, and other study team members. The content of these reports will be determined by the CC Statistician, in consultation with the SPI, and other study team members.

The procedure for locking the database prior to final analysis will be detailed in Section N of the study DMP, in accordance with the CCs *SOP DSD-001: Development of a Data Management Plan* (see Appendix C) and *SOP DSD-405: Data Lock*. Briefly, the Oracle Clinical (OC) data will be locked and the final SAS datasets will be generated at the end of the study. Prior to locking the database, the Clinical Data Manager (CDM) or designee will ensure all data is complete and clean. Then, the CDM will obtain approval from the Project Manager to proceed with the data lock. The CDM will then direct the Database Development Manager to lock the database. The date and time of database lock will be documented. All team members will receive written notification from the CDM or designee when the database lock is complete.

No masking or coding is anticipated for this study.

### **15.5 Study Records Retention**

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH or longer as dictated by local IRB or state laws/regulations.

As outlined by IRB regulations, data will be destroyed in an appropriate and safe way after three years from the conclusion of the study. The file connecting subjects' names with their unique identification number will be kept in a password-protected file by the CC and on the GPI's computer for a minimum of three years, in accordance with IRB regulations, before being securely erased.

### **15.6 Protocol Deviations**

A protocol deviation is any noncompliance with the clinical study protocol and good clinical practice principles. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All deviations from the protocol must be addressed in study subject source documents and promptly reported to NIDCR and the local IRB, according to their requirements.

Any protocol deviation that is reportable to an IRB must also be reported to NIDCR. NIDCR defers to the IRB for reporting time-frame requirements. Once a protocol deviation has been reported to an IRB, action must be taken to report the deviation to NIDCR. If the IRB overseeing the study protocol requires annual reporting of protocol deviations to their IRB, that reporting frequency is acceptable to NIDCR. At the time of each DSMB review, all previously unreported protocol deviations must be reported to the DSMB independent of when they are reported to IRBs.

## 16 PUBLICATION POLICY

This study will comply with the [NIH Public Access Policy](#), which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive [PubMed Central](#) upon acceptance for publication. All study personnel are required to read in its entirety and agree to abide by the network's "Data Analysis, Publications, and Presentations Policies" document. The current version of this policy is always kept at the network's public web site at <http://nationaldentalpbrn.org/publication.php>.

## 17 LITERATURE REFERENCES

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15. Network Study “Longitudinal follow-up of questionable occlusal caries lesions”. Further details about this study are available at The National Dental PBRN web site at <http://nationaldentalpbrn.org/study-results.php>.
16. Information on attaining assent from a minor. <http://answers.hhs.gov/ohrp/questions/7267>.

## **APPENDICES**

- Appendix A1: Schedule of Events (Pilot Phase)
- Appendix A2: Schedule of Events (Full study)
- Appendix B. Quality Management Plan
- Appendix C. Data Management Plan
- Appendix D: Study Timeline
- Appendix E: Statistical Analysis

### Appendix A1: Schedule of Events (Pilot Phase)

For this study, a dental exam will be performed and if the patient qualifies, he/she will be presented with the consent form. If participating, the practitioner will fill out the pre-treatment questionnaire, use the device (if in the device arm), and complete the post-treatment questionnaire. The questionnaire includes questions about caries risk, demographic and lesion characteristics, and final treatment.

Procedures	Pre enrollment (S -0)	Baseline (S0)	Pre-intervention Phase (S1=Complete within approx. 2 weeks following S0)	Intervention Phase (S2=Complete within approx.2 ± 1 week following S1)	Post Intervention (S3=Complete within approx. 1 week following S2)
	← Practitioner Involvement →				
Practitioner Recruitment and Enrollment	X				
Pre-Baseline Diagnostic Vignette	X				
Practitioner and Office Staff Training		X			
Verify Patient Inclusion Exclusion			X	X	
Data Collection			X	X	
Practitioner Randomization			X		
Device Set up and Training (if randomized to device arm)				X	
Post Study Diagnostic Vignette					X
Post Study Questionnaire					X
			Patient Involvement		
Informed Consent			X	X	

### Appendix A2: Schedule of Events (Full study)

For this study, a dental exam will be performed and if the patient qualifies, he/she will be presented with the consent form. If participating, the practitioner will fill out the pre-treatment questionnaire, use the device (if in the device arm), and complete the post-treatment questionnaire. The questionnaire includes questions about caries risk, demographic and lesion characteristics, and final treatment.

Procedures	Pre enrollment (S -0)	Baseline (S0)	Pre-intervention Phase (S1=Complete within approx. 6 weeks following S0)	Intervention Phase (S2=Complete within approx.8 ± 2 weeks following S1)	Post Intervention (S3=Complete within approx. 2 weeks following S2)
	← Practitioner Involvement →				
Practitioner Recruitment and Enrollment	X				
Pre-Baseline Diagnostic Vignette	X				
Practitioner and Office Staff Training		X			
Verify Patient Inclusion Exclusion			X	X	
Data Collection			X	X	
Practitioner Randomization			X		
Device Set up and Training (if randomized to device arm)				X	
Post Study Diagnostic Vignette					X
Post Study Questionnaire					X
			Patient Involvement		
Informed Consent			X	X	

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## Appendix B: Quality Management Plan

This Study Quality Management Plan organizes the plans for QA/QC across the SOCL Study Protocol Study Timeline and Study Activities. Some of the planned QA/QC is described in the main text of the protocol. Specifically, the QA/QC for Data Collection and Management is described in Section 13 above. The Data Management Plan described in Appendix C below will contain the specific plan for Quality Management of Data Collection and Management.

The following is a summary of the QA/QC activities that are planned for each key study activity:

1. **Practitioner Recruitment, Training, and Enrollment:**
  - a. The RCs who will be recruiting practitioners within each region will work with the practitioners to assure that they understand the expectations of them for the study and assure the quality of practitioner recruitment and enrollment.
  - b. The Study Manager will ensure the proper enrollment of practitioners and their locations' study personnel into the IRB system. Through this activity, the Study Manager will also provide QA/QC of the recruitment across regions according to the protocol and procedures, and will help troubleshoot recruitment/enrollment issues.
  
2. **Subject screening and enrollment:**
  - a. Proper training of the practitioners by the RC on the protocol and procedures as outlined in the study Manual of Procedures (MOP) is a planned QA activity. This will assure that the practitioners are ready to conduct the subject screening and enrollment in accordance with the protocol.
  - b. The RC will be a resource for the practitioners and study personnel to ask questions during subject screening and enrollment. The Study Manager will keep a log of problems encountered and solutions across regions and RCs. This will assure consistency of solutions to problems encountered by practices across RCs and Regions. The RC will also use the log to create a regularly updated 'Frequently Asked Questions' document that will be available to all practices, so that they have a resource for finding information and solutions for commonly encountered problems.  
As the practitioners and each practice are anticipated to be busy dental practices, the study is designed to provide the practitioners with extensive support of the RC, the Study Manager, and the CC. Where possible, QA/QC will be assisted by or performed by the RC, the Study Manager, or the CC to allow the practitioner efforts to be focused on subject enrollment. Each practice will maintain an Eligible Patient Screening Log which captures whether a patient consented or not and will send a copy to the RC regularly, during Enrollment for Intensive Data Review. If a patient provides consent the date of consent will be recorded and if consent is not provided the reason for not consenting will be recorded.
  
3. **Data Collection:**
  - a. The RAS will perform a QC review of the data collected on the first patient enrolled by each practitioner and provide feedback to the practitioner and practice. This early QC is a key component of assuring the quality of data collection at the practice, and data entry at the RAS.
  - b. Further details regarding QA/QC of data collection are contained in the MOP..

**4. Data Analysis and interpretation:**

- a. All data analyses for presentations and publications will be verified by “secondary” programmer/statistician for 1) validity of statistical programming to correspondence with interpretation, and 2) appropriate analytic results (output) are correctly presented in presentation and/or publication.

**5. Manuscript Writing, conference presentations:**

- a. The National Dental PBRN has a Publications and Presentations policy. The SPI will assure that this policy is followed for any manuscripts and conference presentations. This policy assures the quality of all National Dental PBRN manuscripts and presentations through the requirement of specific quality control steps prior to publication of any manuscript or other external publication/presentation. Specifically the policy requires review and approval of manuscripts and presentations by the Publications & Presentations Committee.

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## **Appendix C: Data Management Plan**

The CC, for the study, Decision Aids for the Management of SOCL has Standard Operating Procedures (SOPs) which require the development of a Data Management Plan for each project for which the CC provides Data Management services. The CC SOPs require that the Data Management Plan be developed according to a standard template containing the following sections, where applicable:

### **Approval Signatures**

### **Table of Contents**

### **Abbreviations and Definitions**

### **Dynamic References**

#### **1. Introduction**

- 1.1 Protocol Summary
- 1.2 Data Management Services Plan

#### **2. System and the Underlying Clinical Database**

#### **3. Network Directories**

#### **4. Data Validation Process**

- 4.1 Univariate Alerts
- 4.2 Multivariate and Cross-Module Alerts
- 4.3 Edit Checks Development and Approval

#### **5. Verification of System Setup and Implementation**

- 5.1 System Specifications
- 5.2 User Acceptance Testing

#### **6. Data Entry and Data Cleaning**

- 6.1 Pre-Requisites for Site Data Entry
- 6.2 Granting Access to The Production Version of the System
- 6.3 Entering Data
- 6.4 Data Security
- 6.5 Quality Control Procedures
- 6.6 Query ("Discrepancy") Generation

#### **7. Loading Electronic Files**

#### **8. Medical Coding**

- 8.1 Adverse Event/Medical History Coding
- 8.2 Medication Coding

#### **9. System Exported Database**

#### **10. Reports**

#### **11. SAE Reconciliation**

#### **12. Changes to a Production System**

### **13. System Closure**

- 13.1 Closure Checks
- 13.2 Quality Assurance Audit and System Lock
- 13.3 System Unlock

### **14. Data Archiving and Provision of Final Materials to Sponsor**

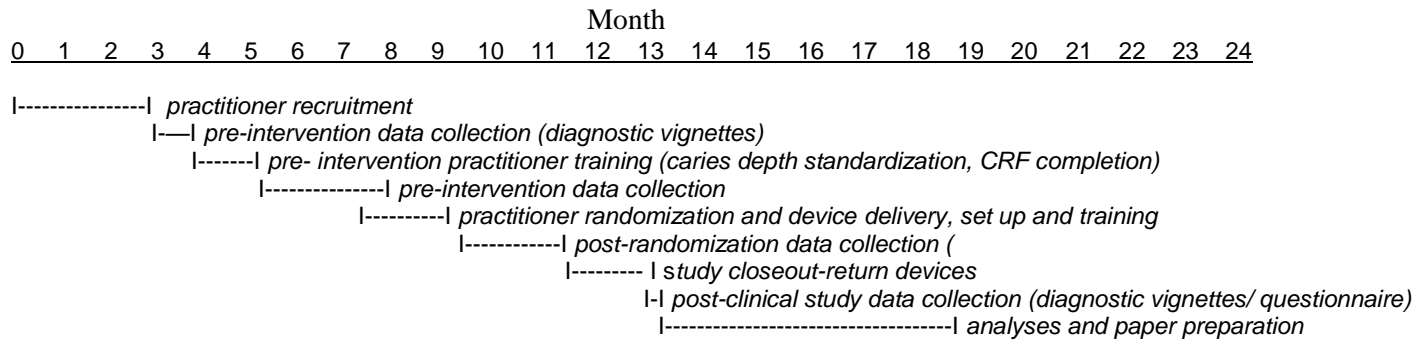
- 14.1 Database Archive
- 14.2 Study Materials and Data Transfer

### **15. DMP Associated Documents and SOP Reference Guide**

### **Appendices**



## Appendix D: Study Timeline



## Appendix E: Statistical Analysis

The primary analysis framework will be based on mixed-model logistic regression analysis, implemented with generalized estimating equations (GEE) to account for correlation among the clusters of observations made by the same practitioners and to provide valid comparisons among the study groups.

Initial exploratory analyses will be conducted for the entire study data set, in order to characterize the empirical distributions of each variable, to identify possible errors in the data, and to evaluate the proportion of missing values. Since the data for Specific Aims 1 through 3 are collected at a single time point, patient-level missing values are anticipated to be unlikely, compared to concerns that arise in studies that include follow-up. If a patient rescinds consent during the study procedures, the practitioner can recruit a replacement patient, as this will not affect the randomized intervention assignment.

The analyses will include all observations that have valid values for the variables in each of the respective analyses. No attempt to replace or impute values that are missing is planned, as this would require assumptions related to the associations that are to be investigated, and could allow pre-analysis expectations to influence the study findings. If a substantial number of missing values is observed, the distribution of these will be evaluated in order to determine whether the missingness can be reasonably assumed to be at random. If this situation holds, then missing values would reduce power, but would not bias the estimates. If missing values are found to occur non-randomly, then the mechanism leading to missing values must be taken into account in the analysis model, for instance, by including variables that are found to be related to missingness. The proposed sample size anticipates that some values may not be obtained, and provides for adequate power despite having up to approximately 20% of observations having missing values for some variables, depending on the differences and level of ICC that are actually observed in the study.

For evaluation of differences in proportions of lesions treated operatively among the intervention groups, the analysis data set will include all SOCLs that are enrolled by the study practitioners. The outcome variable for this analysis will be a dichotomous variable indicating whether the SOCL was treated operatively. Proportions of SOCL treated operatively will be calculated for each study arm. Confidence intervals, adjusted for correlation within clusters (practitioners), will be estimated from the GEE models. Statistical tests for differences in proportions among the three study arms will be based on Type III tests from the GEE analysis, controlling for the effect of clustering by practitioner. An indicator variable representing the study arm will be included as a fixed effect in this model, and a term representing the individual practitioners will be included as a random effect. The effect of regional site will be evaluated as a fixed effect, and will be included in the model if it explains a statistically significant portion of the observed variation in the outcome variable. The two pre-planned comparisons of the device versus no-device arms will be evaluated using contrasts, and will be tested using Chi-square tests of score statistics. Because these are pre-planned comparisons, each of these tests will be conducted at the 95% confidence level, using per-comparison error rates.

For the comparison of proportions of lesions treated operatively that have caries extending into dentin, the analysis data set will include all SOCLs that were treated operatively by the study practitioners. The outcome variable will be a dichotomous variable indicating whether the lesion extended into the dentin. The analysis will be identical to that utilized for Aim 1, except for the reduced analytic sample. GEE-based mixed-model logistic regression will be used to estimate confidence intervals for proportions of SOCLs extending into dentin, controlling for clustering by

practitioner and, if needed, for regional differences. Two pre-planned comparisons will be conducted using contrasts to compare each of the device study arms with the no-device arm.

The analysis data set for identification of clinical characteristics of SOCLs that predict caries extending into the dentin will include all SOCLs that were treated operatively by the study practitioners. The outcome variable will be a dichotomous variable indicating whether the lesion extended into the dentin. The primary statistical model will be mixed-model logistic regression, implemented with GEE in order to account for clustered observations. Clinical characteristics that will be evaluated as potential predictors of caries extending into dentin are luster, color, roughness on examination with explorer, tooth position (molar or premolar), and patient dental history variables. A term representing the individual practitioner will be included in the model as a random effect. Study arm, region and terms representing each of the clinical characteristics of the lesions will be included as fixed effects. Initial analyses will be conducted considering each of the clinical characteristic variables singly, along with region and the random effect term, to determine whether there is a significant “univariate” association between the potential predictor and the outcome. Following this series of analyses, a multi-variable approach will be used to evaluate the joint association between the clinical characteristics and the outcome. This analysis will include the practitioner term as a random effect, region, and all of the clinical characteristics that were associated with dentin involvement, at  $p < 0.10$ , in the “univariate” analyses. The liberal significance level, using  $p < 0.10$ , will be used in order to allow for the possibility that some variables may become more significant in the multivariable approach than in the “univariate” analyses. Further analysis may be conducted, in which non-significant predictors are removed from the multivariable model in order to obtain a more concise prediction model.

Additional descriptive analyses will be conducted to evaluate possible association of practitioner and patient characteristics with outcome measures or other study variables. Depending on the specific structures of these auxiliary analyses, appropriate analysis models may include hierarchical methods, or single-level approaches such as contingency table analysis using the Chi-square statistic or ordinary analysis of variance or logistic regression analyses.

For evaluation of differences in proportions of lesions treated operatively among the intervention groups, the analysis data set will include all SOCLs that are enrolled by the study practitioners. The outcome variable for this analysis will be a dichotomous variable indicating whether the SOCL was treated operatively.

For the comparison of proportions of lesions treated operatively that have caries extending into dentin, the analysis data set will include all SOCLs that were treated operatively by the study practitioners. The outcome variable will be a dichotomous variable indicating whether the lesion extended into the dentin.

Exploratory statistical analyses will be conducted to examine changes in practitioners’ rates of operative treatment of lesions during the pre-randomization run-in period versus their rates during the post-randomization intervention period. Further analyses will be conducted to evaluate possible associations between pre- to post-randomization changes in practitioners’ rates of operative treatment and variables representing practitioners’ perception of changes in the decision-making process. This analysis will be conducted using the practitioner as the unit of analysis, and will utilize a mixed-model analysis of variance approach to evaluate changes in rates and to compare mean changes among the intervention groups, accounting for repeated observations for the practitioners.