

CONTEXT WITHIN WHICH THE STUDY WILL BE CONDUCTED

The Dental-Practice Based Research Network, DPBRN, is a group of dental practices that have been linked together to investigate research questions and to share experiences and expertise. A comprehensive description of DPBRN is provided in the "parent" U01 grant application, which has already been provided to the DPBRN Protocol Review Committee. An additional resource is DPBRN's web site at <http://www.DentalPBRN.org>.

Because DPBRN is committed to being guided by the needs and desires of practitioners, the intent for its studies is to address topics that are of direct relevance to general dentists in clinical practice, to conduct studies that are simple in design and which require minimal training, and to conduct studies that do not unduly interrupt the busy flow of daily clinical practice. Ideas for research projects come from practitioner-investigators in the network, and a topic of interest that has been mentioned numerous times in the enrollment questionnaire and orientation sessions is the diagnosis and treatment of questionable occlusal lesions. Although this is a problem faced by many practitioners, there has been little careful clinical research and no evidence-based assessments regarding the phenomenon of questionable lesions [Bader, 2001; Bader, 2006]. DPBRN offers an excellent opportunity to conduct such a study.

FOCUS OF THIS STUDY, "Questionable Occlusal Carious Lesions"

This study will focus on questionable occlusal lesions. The term "questionable" is defined as a tooth with no cavitation (no continuity break in the enamel) and no radiographic radiolucencies, but the presence of caries is suspected due to roughness, surface opacities, or staining. The characteristics of these lesions, the patient's baseline caries risk, as well as the 24-month outcomes of their treatments, both restorative and preventive, will be examined.

It is important to note the distinction between the terms "questionable" and "hidden". Hidden lesions also appear to be intact clinically, but have detectable caries by radiographic methods. It is for this reason that we are randomly reviewing 5 radiographs from each practitioner baseline radiographs (taken that day or up to six months prior) as part of this study.

This study will build on DPBRN Study 2 "Reasons for placements of restorations on previously unrestored surfaces". DPBRN Study 2 only included surfaces that were restored, and the reason for the restoration and the type of restorative material used was examined. In Study 6, DPBRN will investigate the process involved when making decisions about treatment of questionable lesions, as well as determine if there are any associations between lesion progression (or depth, if opened) and clinical characteristics and baseline risk assessment. The results of Study 6 will also be compared with responses from the DPBRN Study 1 questionnaire ("Assessment of Caries Diagnosis and Caries Treatment") that practitioners will have completed prior to beginning DPBRN Study 6, which records the practitioner's caries diagnoses and treatment plans used in their practice. The information gathered from the DPBRN Study 1 questionnaire and this study will link practitioners' expressed views in hypothetical scenarios (from DPBRN Study 1) with their actions in specific clinical situations on real patients in their practices.

This study allows us not only to quantify the prevalence of these lesions, but also to observe and follow their treatment over a 24-month period. Due to the range of aggressiveness among participating practitioners, it is likely that some questionable lesions will not be immediately opened. The 24-month follow-up permits an assessment of the outcomes of conservative treatment, information that is almost entirely absent from the literature. Regression of 24-month status against pre-operative status and against preventive intervention(s) should identify useful predictors for 24-month "survival" (i.e., non-progression) of questionable lesions. For the lesions that are opened, this study will allow us to associate pre-operative status (clinical characteristics and risk assessment) and subsequent lesion depth.

A. SPECIFIC AIMS:

Specific Aim 1: To quantify the prevalence of questionable occlusal carious lesions in permanent teeth in the first 100 consecutive eligible patients of DPBRN practitioner-investigators.

Rationale: Anecdotal reports suggest that the prevalence of questionable lesions has increased. To date, there has been no literature regarding the prevalence of questionable lesions; therefore, determining the prevalence of these lesions justifies the importance of this project. Questionable lesions have always been difficult for practitioners to make a definitive diagnostic decision. In light of literature suggesting that progression has slowed, there is more opportunity to evaluate the lesion over time rather than taking an early surgical approach.

Specific Aim 2a: For unopened questionable occlusal carious lesions, to test the hypothesis that the patient's baseline caries risk is significantly associated with "progression" (i.e., change in perceived caries status) during 24 months of follow-up.

Specific Aim 2b: For opened questionable occlusal carious lesions, to test the hypothesis that the patient's baseline caries risk is significantly associated with caries depth.

Rationale: To date, there have been no studies on questionable lesions that take into account the patient's risk factors. Although risk assessment is a vital part of the clinical decision-making process [Zero, 2001; Bader, 2001; Bader 2003; Bader, 2005; Tranæus, 2005; Rindal, 2006], there have been no studies that have linked caries risk to lesion depth. Question #14 on the Data Collection Form will record information such as: current and past lesions, oral hygiene, access to fluoride, diet, and recall care. Question #11 will record the practitioner's assessment of lesion status at baseline and at 24 months using the following categories: suspect caries, but not sure; inactive caries; active caries, limited to the enamel; and active caries, into the dentin.

Past studies have indicated that approximately 50% of all opened questionable lesions have caries into the dentin. Question #17 will record the baseline lesion depth when opened using the following categories: inactive caries; no caries; caries in the outer ½ of enamel; caries in the inner ½ of enamel; caries in the outer ⅓ of dentin; caries in the middle ⅓ of dentin; caries in the inner ⅓ of dentin; and other.

Specific Aim 3a: For unopened questionable occlusal carious lesions, to test the hypothesis that the baseline clinical characteristics are significantly associated with change in caries status during 24 months of follow-up.

Specific Aim 3b: For opened questionable occlusal carious lesions, to test the hypothesis that the baseline clinical characteristics are significantly associated with caries depth.

Rationale: To date, there have been very few studies regarding clinical characteristics and lesion progression of questionable occlusal carious lesions. Question #7 of the Data Collection Form records the baseline clinical characteristics, including the luster and color. Question #11 will record the practitioner's assessment of lesion status at baseline and at 24 months using the following categories: suspect caries, but not sure; inactive caries; active caries, limited to the enamel; and active caries, into the dentin.

Question #17 will record the baseline lesion depth when opened using the following categories: inactive caries; no caries; caries in the outer ½ of enamel; caries in the inner ½ of enamel; caries in the outer ⅓ of dentin; caries in the middle ⅓ of dentin; caries in the inner ⅓ of dentin; and other.

Because this project is a practice-based study, restorative dentistry in 'real life' situations will be recorded. The present study does not intend in any way to influence when or why restorations should be placed.

B. BACKGROUND AND RATIONALE:

B.1. The occurrence of questionable occlusal carious lesions may have increased

A majority of patient contact time spent by DPBRN practitioner-investigators (p-is) in general dental practice deals with restorative dentistry and its associated diagnosis, as determined from the enrollment questionnaires completed by about 1,100 DPBRN p-is (www.DentalPBRN.org). Restorative dentistry is; therefore, the major workload in general dental practice and it covers most of the treatment performed on patients.

The rate of progression of cavitated dental caries has lessened dramatically in recent years, in part due to the advent of fluoride [Sawle, 1988]. As the rate of progression has slowed, the prevalence of occlusal lesions with an intact surface but with sub-surface demineralization has increased [Sawle, 1988]. There are essentially two types of such lesions. In “hidden caries”, demineralization has progressed to the point where it is detectable radiographically. In “questionable caries”, a lesion may or may not exist, but if it is present, demineralization is at a relatively early stage, and is not detectable radiographically. If the surface is intact, and there is no radiographic sign of demineralization, both the presence and depth of any lesion will be difficult to detect [Sawle, 1988; Ketley, 1993; Pitts, 1997; Ouellet, 2002].

Changes in surface texture, luster, color and shadowing have been the traditional means for a diagnosis of caries under these circumstances [Sawle, 1988; Bader, 1993; Ketley, 1993; Pitts, 1997; Ouellet, 2002]. These lesions have become an important part of daily clinical practice; however, to date, there have been very few studies regarding questionable carious lesions, virtually no clinical evaluations of the progression of questionable lesions over time [Bader, 2006], and no studies depicting the prevalence of these lesions. Since carious lesions have the ability to arrest and possibly reverse, determining how often these lesions are being seen in practice and learning more about their characteristics and patient risk assessment are important steps in order to manage these lesions without unnecessary surgical intervention. We will determine prevalence by looking at the first 100 consecutive patients in each office.

B.2. Linking Baseline risk assessment to lesion depth and progression

Risk assessment is a vital part of the clinical decision-making process [Zero, 2001; Bader, 2001; Bader 2003; Bader, 2005; Tranæus, 2005; Rindal, 2006]. In some instances, questionable lesions may only require preventive care in low-risk patients. For high-risk patients, these same lesions may require more aggressive care in the form of surgical intervention; i.e., dental restorations [Christensen, 2000; Pitts, 2004]. Non-invasive treatment of caries involves education and encouragement of behavioral changes to the individual patient with emphasis on plaque control, the use of fluorides, and dietary modification [Kidd, 2003]. The need for restorative dental treatment is to a large extent dependent on the oral hygiene, dietary habits, and access to fluorides. Carious lesions can be arrested if proper oral hygiene is maintained [Nyvad, 1997].

Many factors play a role in establishing a patient’s risk for developing carious lesions [Stewart, 1991]. In a review of published data, it was indicated that the presence of active caries lesions and many restorations was a good measure of the risk for future lesions provided the oral environment is unchanged [Anusavice, 1995]. Treatment planning, including caries diagnosis, must take these factors into consideration, including the patient’s condition and preferences [Ismail, 2004].

It is for these reasons that Question 14 of the data collection form will be linked to the depth of the lesion, if opened, or the progression of these lesions (defined as a change in the clinician’s assessment of lesion status), if treated preventively. The Data Collection Form will focus on patient characteristics including: current and past lesions, oral hygiene, access to fluoride, diet, and recall care. This information will be recorded on 50 consecutive questionable lesions in each practice. The data collection form includes the following selection for those

lesions that are opened: inactive/remineralized caries; no caries; caries in the outer $\frac{1}{2}$ of enamel; caries in the inner $\frac{1}{2}$ of enamel; caries in the outer $\frac{1}{3}$ of dentin; caries in the middle $\frac{1}{3}$ of dentin; caries in the inner $\frac{1}{3}$ of dentin; and other. Inactive/remineralized caries will be defined as caries that is smooth and shiny with a texture that is hard when a probe (explorer) is moved across the surface [Grøn, 1973; ten Cate 1983,1992;Thylstrup, 1994; Ekstrand, 2005].

B.3. Linking clinical characteristics to lesion depth and progression

There has been some debate on the correlation between clinical characteristics of occlusal lesions and their progression. Some studies have shown that the detection of brown or black fissures is not a useful indication of lesion progression. In a study by Francescut, 57% of teeth with dark brown to black discolored fissures showed either no caries or caries limited to the outer $\frac{1}{2}$ of enamel [2003]. Steiner, on the other hand, suggested that brown or black stained fissures were more likely to be indicative of carious lesions [1998]. One study also showed that 42% of yellow to light brown lesions and 27% of opaque lesions were found to have caries in the middle $\frac{1}{3}$ of dentin [Francescut, 2003]. Practitioners can learn valuable information if associations exist between clinical characteristics and lesion progression and/or depth. Right now, there are no clear guidelines for managing these lesions [Clinical Research Associates, 1999].

The Data Collection form, in addition to descriptions, will also include photos. These photos depict various types of questionable lesions such as: white spots; discoloration (light brown, dark brown); and lesions covering some, most, or all of the occlusal surface. This information will be recorded on 50 consecutive questionable lesions in each practice.

By following these lesions for 24 months, a link can be made between the initial clinical characteristic of a lesion and the status, including the lesion depth if intervened surgically. Based on past studies, we suspect that close to 50% of the lesions that are opened will reveal caries into the dentin.

B.4. Studies related to questionable occlusal carious lesions

In a study by Ouellet [2002], extracted third molars were diagnosed by three clinicians using a mirror and explorer, as well as a laser fluorescence device (DIAGNOdent®) to determine the depth of questionable lesions. When the 100 teeth were sectioned, 41% had caries at or below the DEJ. The DIAGNOdent® had high sensitivity (up to 94%) but a lower specificity (55%). The clinicians' sensitivity ranged from 40-82% and the specificity ranged from 78-85%, which clearly shows the variations in how they diagnose these types of lesions. With this study, though, the patient's risk was not considered, which could have impacted their decisions.

In a study by Hamilton [2002], participants with questionable lesions were randomly assigned to an early treatment group (receiving air abrasion) and a control group (no treatment). In the early treatment group, less than 50% of the teeth with questionable lesions had progressed into the dentin. After 2 years, the probability of caries occurring in the control group was 16%. This study also found that there was a strong correlation between pit and fissure feel and caries penetrating into the dentin ($p=0.0149$). We have included queries about use of an explorer in the Data Collection Form for those practitioners who use dental explorers in their daily clinical practice.

The purpose of the Hamilton study was to compare early treatment vs. no treatment in questionable occlusal carious lesions. The results illustrated that there was no significant difference in the conservation of tooth structure between the early treatment and control groups, as well as an increased risk of unnecessary surgical intervention if the tooth is opened immediately, before any signs of progression are observed. With this study, however, no data were presented regarding practitioner aggressiveness, which is important because different levels of aggressiveness in opening questionable lesions can make a difference in outcomes. DPBRN Study 6 will be linking practitioner's thoughts with actions by filling out the "Assessment

of Caries Diagnosis and Caries Treatment”. It is also important to note that the Hamilton study did not collect information on lesion characteristics that could be analyzed for likelihood of caries into the dentin. DPBRN Study 6 will accomplish this through Questions #7,8,9,10, and 13.

Although these studies had differences in validation methods, they all showed the likelihood of questionable lesions penetrating the dentin to be about 50%, making the decision of whether to intervene surgically or not a difficult one.

B.5. Filling in the gaps in knowledge

Performing a study such as the one proposed as DPBRN Study 6, that not only looks at the practitioner’s identification, but also the risk assessment of the patient, clinical characteristics of the lesion, and subsequent treatment, will help fill the gaps of knowledge. It is important to note that although the extant studies looked at how practitioners diagnose these lesions, no study recorded how the practitioners would treat them in a daily clinical setting. This is an important feature of the proposed DPBRN Study 6 because some practitioners are more aggressive than others in intervening surgically in the presence of uncertainty. It is likely that among the questionable lesions that are “opened,” some will display no detectable caries, some will display caries contained in the enamel, and some will display caries penetrating into the dentin.

Figure 1 [Bader, 1997] illustrates a conceptual model of a practitioners’ treatment decision-making. This model includes information such as visual, tactile, and radiographic signs, as well as the patient’s risk assessment, all of which will be captured with the proposed study’s data collection form. Currently, limited information is available from general dental practice in the U.S. about the stage in the development of caries lesions that is considered appropriate for surgical intervention. According to a survey of the teaching of cariology in North American dental schools [Clark, 2001], about two-thirds of the schools advocated surgical intervention when lesions have reached dentin, mainly the D1 level - the outer third of dentin, with the aid of radiographs. The remaining one-third of the schools taught the treatment of enamel lesions operatively, mainly E2 lesions. In Florida, where the clinicians are graduates from dental schools across the US, almost 60% treated enamel lesions operatively, including 11% E1 lesions, and only about 40% waited until the caries lesions reached dentin [Mjör, 2004]. Browning and Dennison found that 40% of all restorations in Western countries are placed due to primary caries, namely small carious lesions [1996]. This may be based on tradition and uncertainty about caries progression among clinicians who may adopt the “better safe than sorry” approach and operatively treat lesions that may be arrested by preventive measures. Many times, the tooth is prepared based on the philosophy of “extension for prevention” and the needs of the restorative material used, not necessarily the health of the tooth [White, 2000].

By recording information over a 24-month period on the clinical characteristics of the lesion (both visual and tactile), the baseline assessment of the patient’s risk, and the subsequent treatment and outcome, the associations inferred will ultimately provide useful information to clinicians regarding which characteristics offer more valid information about the caries status of questionable lesions. If there is strong evidence regarding the frequency and progression of questionable lesions, non-invasive management strategies would be more widely accepted [Bader, 2006].

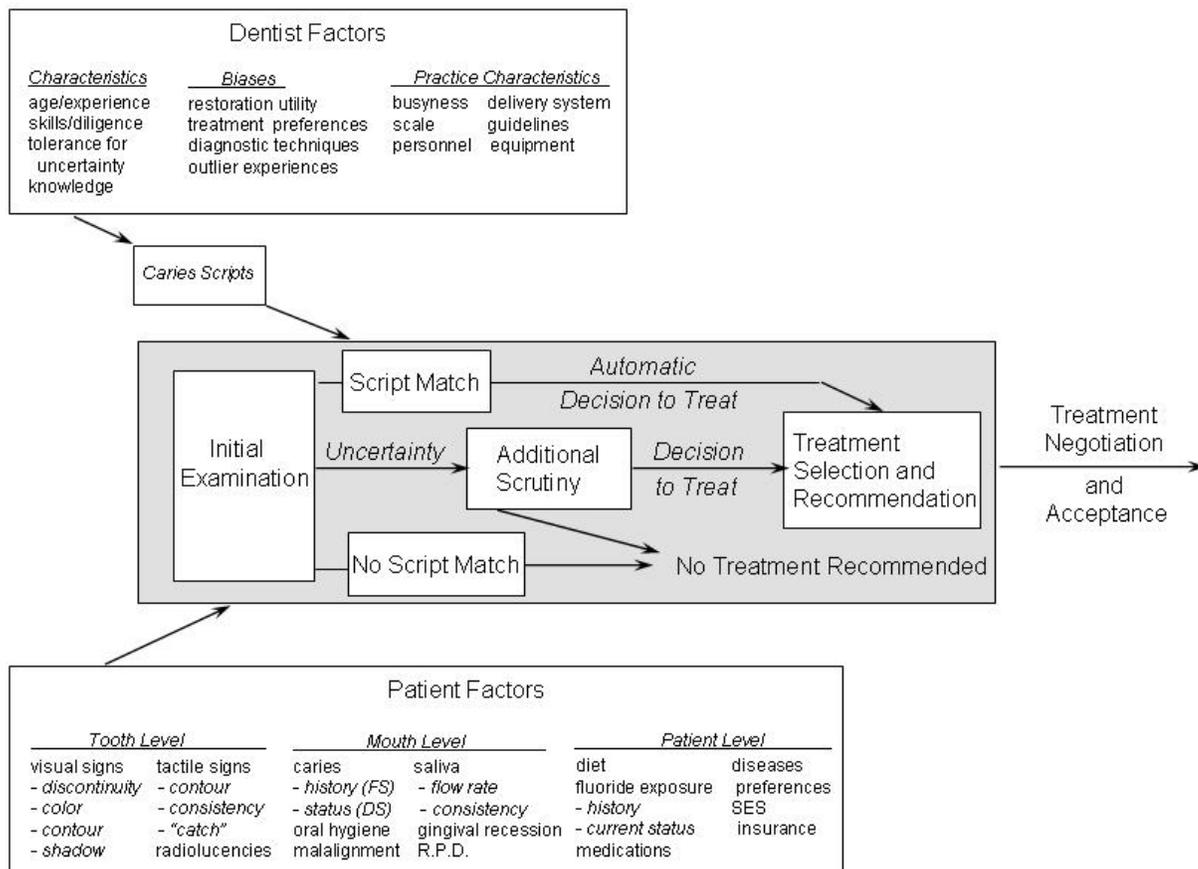


Figure 1. Conceptual model of dentists' caries-related treatment model [Bader, 1997]

C. PRELIMINARY STUDIES

C.1. Preliminary studies in the dental practice-based context conducted by the DPBRN group

The "parent" U01 grant application describes practice-based studies conducted by investigators in the DPBRN group. These studies have been conducted in Florida, the Kaiser Permanente organization, the HealthPartners organization, Alabama, and in Scandinavia. These studies have involved questionnaires completed by dentists in clinical practice, studies involving direct data collection by clinicians, and investigations that make use of data already being collected during the process of daily clinical care. These investigators have now joined forces in a collaborative, well-integrated entity now called the DPBRN.

C.2. Studies preceding this DPBRN study

The information from the "Assessment of Caries Diagnosis and Caries Treatment" questionnaire ("Study 1 questionnaire"), which practitioners will have completed prior to this study, will be used to compare attitudes and opinions related to selected topics in cariology to what treatment is actually done in practice.

As of March 27, 2007, a total of 501 Study 1 questionnaires have been returned, demonstrating that the number of possible Study 6 p-is is already well over the 75 that will be

needed for this study. Furthermore, preliminary results from Study 1 suggest that 22% of dentists are likely to intervene surgically, either invasively or minimally invasively, when occlusal caries on low-risk patients has reached the E1 level. When occlusal caries is diagnosed on low-risk patients at the E2 level, 75% of dentists tend to intervene surgically. The percentages change with proximal lesions: 2% of the dentists in the sample chose to intervene surgically on E1 proximal caries and 37% on E2 proximal caries. These preliminary data show the substantial variation practitioners have with regards to surgical intervention.

D. RESEARCH DESIGN AND METHODS

D.1. Inclusion criteria

Practitioner-investigators must be enrolled in DPBRN, complete an enrollment form and an "Assessment of Caries Diagnosis and Caries Treatment" questionnaire, be certified in Human Subjects Protection, attend or view an orientation session, and do at least some restorative dentistry in their practices as reported on the enrollment questionnaire.

D.2. Selection and recruitment process

A total of 75 DPBRN p-is will be enrolled in this study. The first phase of recruitment letters will be sent to 150 practices that have been pre-selected because they meet one or more targeted criteria: (1) they have racial/ethnic minority dentists or they serve patient populations with a substantial proportion of racial/ethnic minorities; (2) they have female dentists; or (3) they are geographically proximate to the administrative sites for each of the DPBRN regions.

D.3. Discussion of this protocol with practices

Before any data collection begins by an individual practice, DPBRN Project Coordinating staff will speak with each participating practice to explain the protocol for this study. Having this meeting at a time and venue preferred by the practitioner and office staff is the preferred method. Other possibilities may be if the practice has a pre-arranged time for meetings or when no patients are being treated. This mechanism provides an opportunity to address all questions that all staff members might have about the protocol. A brief training manual with photographs will also be implemented to insure standardization. (This manual will be submitted to the IRB upon completion.) Human subjects/informed consent issues will be reviewed, as well as procedures specific to this study. It is important that the clinicians and their staff familiarize themselves with the Data Collection Form, including the inclusion criteria (including the need for baseline and 24-month radiographs), photos, and information for data to be entered and the terms used. The photographs used for question #8 will be placed on a laminated sheet in each operatory for reference. Proper completion of the Data Collection Form will be reviewed with all practitioners and staff in the practice.

D.4. Criteria for determining which restorative materials to record

Only the type of material, not brand names, will be reported.

D.5. Data collection process

The Data Collection Form will be pre-tested by the six practitioner-investigator members of the Executive Committee and their staff members. An additional ten DPBRN practices will finalize pre-testing of all forms. Pre-testing will assess the feasibility of the Data Collection Form in the flow of a busy practice environment, as well as the comprehension and intuitiveness of the classification criteria. We will meet with all of the pre-testers to ensure correct terminology is being used and that all of the characteristics (both descriptions and photographs) that they report using in making their diagnoses are represented in the Data Collection Form.

To meet Specific Aim 1, each p-i should record 100 consecutive patients who present with at least one unrestored, unsealed permanent occlusal surface. The number of such surfaces, as well as the number (if any) of questionable carious lesions, should be recorded on the Consecutive Patient Log. It is realized that it will take some time to record information on 100 patients, depending on the busyness and type of practice. For Specific Aims 2 and 3, each p-i will collect data on 50 consecutive questionable occlusal carious lesions. If the 50 questionable lesions have not been reached with the 1st 100 consecutive patients, the practitioners will be given additional weeks to achieve this number. Our estimate based on previous studies is that about 95% of patients who have questionable carious lesions will consent to be enrolled in the study.

All data will be recorded on both regularly scheduled patients and on patients who show on an 'urgent care' or 'emergency' basis. Consecutiveness is an important part of this study. Therefore, consecutive lesions will be logged, but emergencies and walk-ins, and any other patients for whom the practitioner thinks that availability at 24 months will be problematic can be excused from the request to participate at the practitioner's discretion and log it onto the Consecutive Log. The data on each patient with a questionable carious lesion should be entered on a separate Data Collection Form.

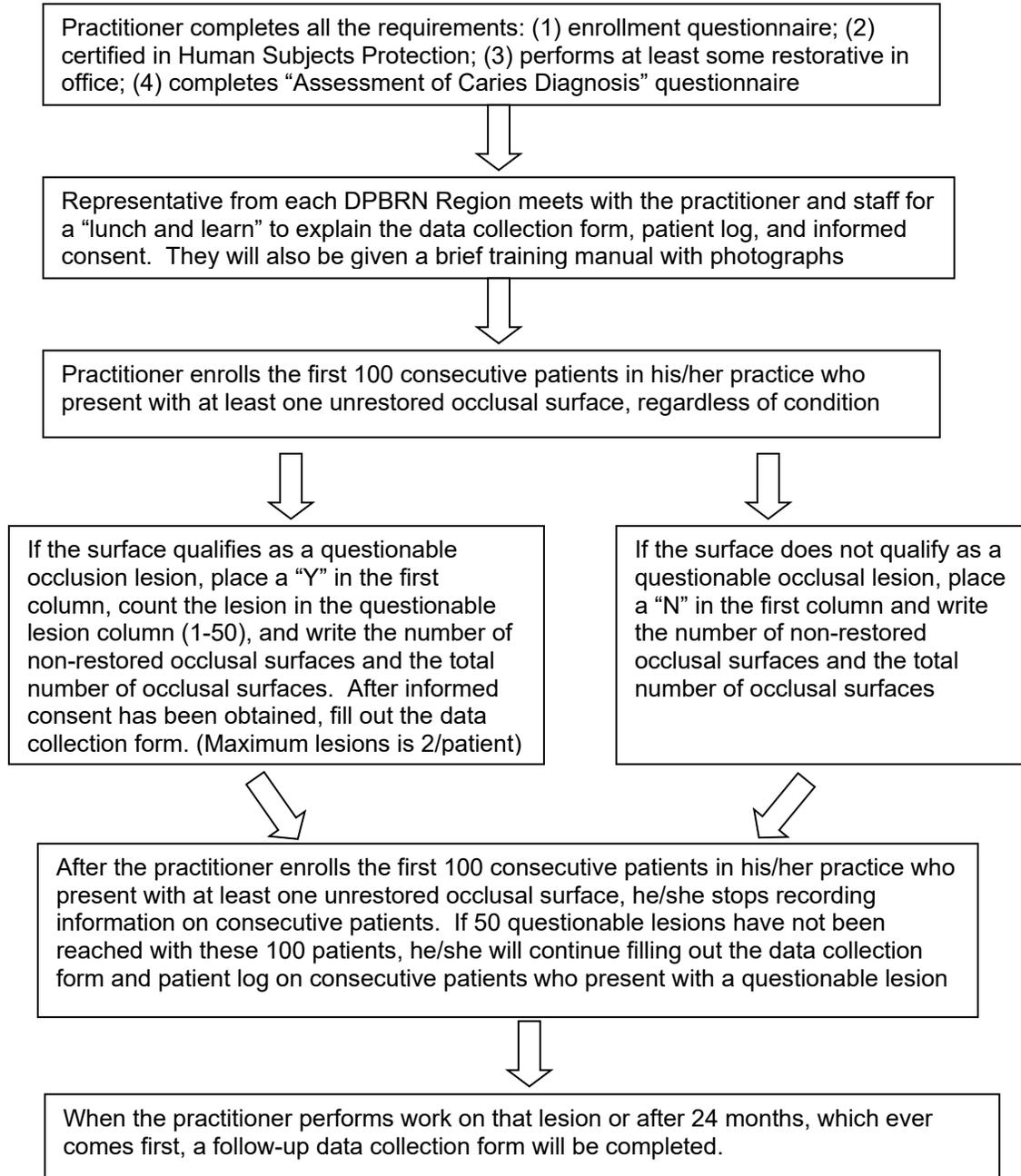
After information on 50 questionable lesions has been recorded, the data should be submitted to the DPBRN Regional Coordinator. The p-is must keep copies of the forms sent to the Regional Coordinator, and these should become part of the patients' treatment records.

The data will be sent to the Coordinating Center via two methods. Dental offices in the Permanente Dental Associates group and in the HealthPartners group will enter the data in a secure web-based portal. The baseline radiographs will be either scanned by the Regional Coordinator or, if electronic radiographs were taken, a print out will be collected on 5 randomly selected patients. These images will be sent to the Coordinating Center where trained dentists will ensure there are no signs of caries in teeth in which the data were collected.

The signed Informed Consent Form and a copy of the Data Collection Form will be maintained in the patient's chart for the Alabama/Mississippi, Florida/Georgia, and Scandinavian regions, but depending on the requirements of each region's Institutional Review Board, DPBRN practitioner-investigators themselves may be required to sign a Practitioner Informed Consent Form.

P-is will be remunerated when the forms for 50 questionable lesions have been submitted or at the termination of data collection for the study. Remuneration will be \$50 per questionable lesion diagnosed and \$25 per questionable lesion diagnosed on the same patient at the same visit thereafter (pending final decision by the DPBRN Executive Committee). Queries from the Regional Center or Coordinating Center regarding illegible or unclear responses must be addressed before any payments will be made. We expect that payments will take up to 8 weeks for processing of paperwork.

D.6. Step-by-step process for DPBRN Study 6



D.7. Data management and quality assurance procedures

Forms sent as hard copy to the Regional Coordinator will be photocopied, with the hard copy, along with the radiograph, sent to the Coordinating Center. Staff at the Coordinating Center will scan these forms and professional data entry staff will use a dual monitor system to view the electronic image on one monitor and enter data into a second. They will be organized into identifiable batches for data entry and two 10% samples of forms will be selected. The first will be re-entered by the original data entry technician to determine intra-rater reliability and the

second by a different technician for inter-rater reliability. If the discrepancy rate for either re-entry sample is above 0.5%, then the full batch will be re-entered. Re-training may be necessary if unacceptable error rates continue to occur.

All electronic data stored for the study will be located on a secure network drive with severely restricted access. All personnel at the Coordinating Center are required to have current IRB and HIPAA training certification and all must sign confidentiality forms. All paper copies are stored in a secured room.

The data will be stored using the current version of ACCESS or SQL database software packages. The database programming staff will work with the Coordinating Center investigators and Network Chair to make sure that the required systems are available on time and function efficiently.

The final dataset and documentation will be prepared by members of the Coordinating Center statistical consulting unit (SCU). Data analysis will be performed by one member of the SCU and subsequently verified by another, using the SAS[®] statistical software system.

D.8. Monitoring recruitment and data collection during the field phase

A DPBRN Regional Coordinator will be assigned responsibility for each practice. Telephone contact will be initiated with each practice during the first week of its participation in the study, with subsequent contact during week 2 and on a monthly basis thereafter. The Regional Coordinator will assess progress in each practice to that date and answer any questions the practice has. Face-to-face meetings will be held with the practice staff at the discretion of the Regional Coordinator assigned to the practice.

D.9. Post-baseline plan

We will perform a 24-month follow-up on all questionable carious lesions found in the study. This follow-up will include collecting information on the current status of the lesion as well as a current radiograph. Patients in this study will understand as part of the Informed Consent process that their questionable carious lesion will be followed for 24 months. If work is performed on the tooth (for example, a restoration or sealant placed), the practitioner will fill out the follow-up data collection form at that time. Practitioners will receive this form at the beginning of the study.

As mentioned previously, the DPBRN Regional Coordinator assigned to the practice will follow-up with the practitioner on a monthly basis to determine if any follow-up data collection forms have been completed. Practitioners will be remunerated \$25 for each follow-up data collection form completed.

D.10. Study design and statistical analysis

The study design is longitudinal, with data consisting of responses to questions regarding frequency, methods of determining, and the treatment for questionable occlusal lesions made by the participating dentist-practitioners based on 100 consecutive patients for each of the dentists. A total of 75 dentist-practitioners will be recruited to participate in the study, based on a stratified convenience sampling scheme that will encourage representation of minority dentists, those who serve patient populations with a large number of racial/ethnic minorities, female dentists, and dentists who are geographically proximate to the DPBRN administrative sites.

The statistical analysis for Aims 1 will consist of calculating point estimates and 95% confidence intervals (CI) for the prevalence of lesions per patient and per surfaces at risk. In calculating the prevalence, we will use the number of consecutive possible surfaces at risk across all patients as the denominator and the number of questionable lesions across all patients as the numerator. The lengths of confidence intervals will be adjusted to account for the correlation among multiple observations made by the same dentists by incorporating an

inflation factor. This inflation factor represents the amount the unadjusted variance estimate needs to be inflated to obtain the correct variance and is given by $IF = [1 + (\text{average number of lesions per dentist} - 1) \times (\text{intraclass correlation})]$.

The basic structure of the dataset contains lesions nested within dentists. Nesting groups compose a measurable component of random variation. As such, regular linear models will not suffice. One method to handle this type of data is the mixed model. Mixed models allow us to include random effects and additional fixed effects [Koepsell, 1998]. The type of mixed model, however, depends on the distribution of the error of the endpoints. When outcomes are continuous in nature, the Mixed Model ANCOVA in one stage is necessary [McCullagh, 1989]. The SAS procedure PROC MIXED [SAS Institute Inc., 1997] easily accommodates this type of model. The one-stage designation implies that rather than calculating group means (e.g. group mean on a subject based measure) and then analyzing, individual subject's responses will be used and adjusted for group membership through the use of random effects. By specifying random effects representing the cluster or group membership, this measurable source of variation can be accounted for and thus remove concern about inflated Type I error. In the General Linear Mixed Models, Restricted Maximum Likelihood (REML) estimation will be used. The REML approach separates the estimation of fixed and random effects. Dichotomous outcomes can also be analyzed via an extension of the mixed model approach or through the use of Generalized Estimating Equations (GEE) [Liang, 1986].

For Aim 2, we will examine the association between patient risk and of questionable occlusal lesions. The study of change in perceived status of questionable occlusal lesions is separated into two aims. In Aim 2a, for unopened questionable occlusal carious lesions we will be examining the association between patient baseline caries risk and progression during 24 months of follow up. Using responses from question 11 at both baseline and at 24 months, we can create a dichotomous variable measuring progression (yes/no). To test the association between baseline risk (Q14) and progression we will use Generalized Linear Models. In Aim 2b, for opened questionable carious lesions we will be assessing the relationship between patient risk and caries depth. In question 17 the depth of the lesion will be recorded as: no caries; inactive caries; outer $\frac{1}{2}$ of enamel; inner $\frac{1}{2}$ of enamel; outer $\frac{1}{3}$ of dentin; middle $\frac{1}{3}$ of dentin; or inner $\frac{1}{3}$ of dentin. These categories exist on a continuum and are ordinal at minimum. As a result of the nature and range of the data and the expected sample size, it is acceptable to use statistical methods typically reserved for traditional continuous data. We will first analyze the association between patient risk and progression using ANOVA. To properly account for multiple lesions within a patient we will use Mixed Models Analysis. Because the outcome of interest is treated as being continuous, the Mixed Model ANCOVA in one stage is necessary [McCullagh, 1989]. An ANCOVA model is preferred because it allows for the adjustment of the baseline value of caries state.

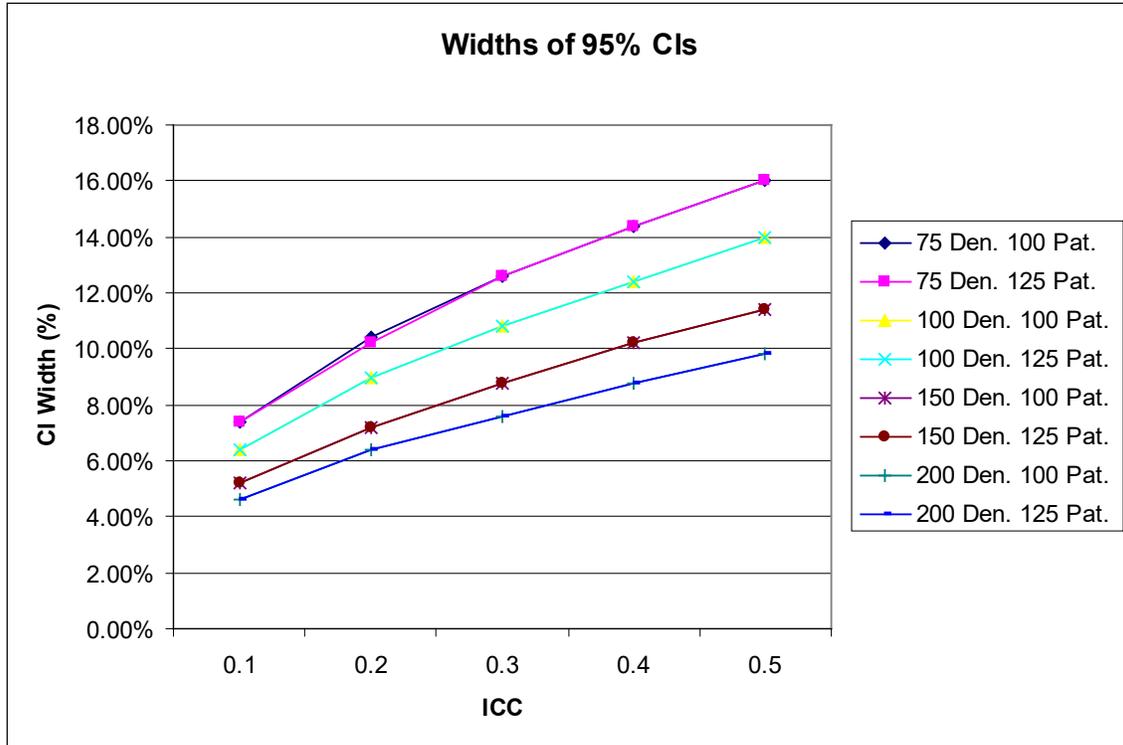
In Aim 3a we will examine the association between practitioner baseline classification of clinical appearance of questionable lesions and progression. Similar to Aim 2a we will use Generalized Linear Models to test the association between clinical characteristics and progression. Likewise for Aim 3b as in Aim 2b we will assess the association between clinical characteristics and caries depth using a Mixed Model ANCOVA.

We will also investigate Aims 2 and 3 using more complex analytic approaches that do not assume a normal distribution, such as multinomial logistic regression. Treating the dependent variable as a categorical variable we can use SAS procedures such as PROC CATMOD to answer questions such as, "Are people categorized as having high risk for caries more likely to have caries in the inner $\frac{1}{3}$ of dentin vs. the outer $\frac{1}{3}$ of dentin?".

D.11. Power considerations

Precision of estimation for the proportion (prevalence) defined in Aim 1 was based on widths of 95% CIs for a proportion. To calculate our cluster-adjusted N we first calculated the inflation factor (IF) and then divided the total sample size (75 dentists x 100 patients=7500 patients) by the IF. To be conservative we used 0.5 as the estimation of p as it will yield the widest CI (greatest variability occurs in the middle of the binomial distribution). The figure shows the widths of CIs for sample sizes of 75, 100, 150, and 200 dentists, with 100 or 125 patients observed per dentist, and ICC values of 0.10 to 0.50. With a sample size of 100 patients for each of 100 dentists, the CI width for an estimated percentage of 50% ranges from 6.4% for ICC = 0.10 to 14.0% for ICC = 0.50. If each of 150 dentists contributes 100 patients to the sample, then the CI width ranges from 5.2% to 11.4% for ICC values of 0.10 to 0.50. With ICC = 0.10, and using 125 patients per dentist and 200 dentists, the resulting 25,000 observations yields a CI of width 4.6% as compared to the width of 5.2% that results from using 125 patients from each of 150 dentists. As is clear from the graph, the precision depends more strongly on the number of dentists and the ICC than on the number of patients per dentist. Because very little precision is gained by increasing from 75 to 100 dentists and only a modest change is gained by increased to 150 dentists, we will recruit 75 dentists to the study.

Consideration has also been given to power to test the hypotheses outlined in Specific Aims 2 & 3. A discussion of the resulting power calculations and assumptions follow. Specific Aim 2 hypothesizes that a practitioner's baseline assessment of a patient's occlusal risk will be significantly associated with progression of questionable occlusal lesions. In considering the complexity of implementation of the study we have chosen to supplement data collection until we have collected data on 50 lesions for each of 75 dentists. Patient risk will be measured by placing the responses in a 3-category scale that will be created based on Question #14. Because we would like to be able to test the difference between any two categories, for Aim 2b we based our power calculations on a two-sided, two sample t-test of means and adjusted the level of significance via a Bonferroni correction for multiple testing. We estimate that lesions will be equally distributed between the three risk categories. As such, we adjusted the number of lesions within each group accordingly. Because there is little known information on which to base power calculations for Aims 2 and 3, an effect size approach was used. Using the aforementioned test, $\alpha=0.01$ (Bonferroni adjusted), and the cluster-adjusted sample sizes corresponding to ICCs ranging from 0.1 to 0.5, we will have 80% power to see effect sizes ranging from 0.333 to 0.703 between any two risk categories. Similarly for Specific Aim 3b, we hypothesize that roughly 50% of lesions will be dark/brown discoloration and the remaining 50% distributed among the other categories. Treating this as two groups again but removing the Bonferroni correction, a two-sided, two-sample, t-test of means and $\alpha=0.05$ reveals we will have 80% power to effect sizes ranging from 0.223 to 0.467 for the associated ICCs (0.1 to 0.5). For Aims 2a and 3a we used a two-sided, two-group continuity corrected Chi-square test of proportions and equal n's. Using the same approach regarding sample sizes and Bonferroni corrections for Specific Aim 2a, we will have 80% power to detect a difference in progression ranging from 17% and 34% between risk groups. Likewise for Specific Aim 3a, we will have 80% power to detect a difference in progression ranging from 11% and 24% in clinical characterization groups.



E. HUMAN SUBJECTS RESEARCH

E.1. Risks to the patients and health care providers

Human subjects' involvement and characteristics. This protocol involves human subjects. The human subjects directly involved in this study are the patients who have sought dental treatment in the p-is' practices, as well as the p-is themselves. The p-is will be recruited from the clinicians enrolled in DPBRN who have met the eligibility criteria specific to this protocol. The p-is will record questionable carious lesions on patients who provide informed consent and who thereby become subjects in this study. Because diagnosis and management will be linked to characteristics of the p-is and their practices, comparisons will be made across practices and by practice characteristics. Participating in the data collection and returning Data Collection Forms may constitute consent by the p-is, but depending on the requirements of each region's Institutional Review Board, DPBRN practitioner-investigators themselves may be required to sign a Practitioner Informed Consent Form.

Sources of materials. Data will be obtained from the Data Collection Forms that each p-i completes. These forms represent 50 questionable carious lesions, which may or may not derive from 50 consecutive patients. Data on these lesions will also be linked to responses that practitioners provided in the Caries Risk Assessment questionnaire, as well as data that practitioners completed for the DPBRN enrollment questionnaire.

Potential risks. The only risk to the p-is and their patients will be the highly unlikely accidental disclosure of health care provider and patients' dental restorative information (if applicable). However, every precaution will be taken to prevent such disclosures. No experimental techniques or materials will be used and the burden on the patients, clinicians and dental office staff, will be the same as that experienced as part of regular dental treatment, except that informed consent will be obtained from patients and the Data Collection Form will be completed for each patient/subject in the study. Information on the restorations placed will be

entered on a Data Collection Form specially designed for this study. The treatment sessions will, therefore, be slightly longer in order to record on these forms the treatment that was provided.

The Data Collection Forms will be coded, kept confidential, and will be stored in a secure place. The DPBRN Executive Committee has closely reviewed the research protocol at each stage of its development, has closely reviewed and pre-tested draft data collection forms, and has provided its unanimous endorsement of the study, the protocol text, and the draft data collection forms.

E.2. Adequacy of protection against risk

Recruitment and informed consent. We will provide the information to p-is and their patients that explains the nature of the study, time commitment involved, any risks involved, and compensation information. We will also answer any questions they may have in a telephone conversation or in face-to-face discussion with them. A specially designed Informed Consent Form will be explained to the patient by the p-is in DPBRN regions where such a form is required. After assurance that the information provided is understood by the patient, the patient and p-i both sign the form, which then becomes part of the patient's treatment record.

Protection against risks. Records will be kept confidential to the extent permitted by law. Only authorized personnel will have access to the data, and all information, whether electronic or in paper form, will be stored in a secure manner. All personnel with access to this information have been certified in human subjects research and HIPAA regulations. This information will not be sold or used for any reason other than research. Results will be published for scientific purposes, but participant identities will not be revealed.

E.3. Potential benefits of the proposed research to the subjects and others

P-is will benefit from the opportunity to reflect their views on caries diagnosis and treatment and gain information on the practice methods of their peers. The p-is will also benefit from a better understanding of how the diagnosis and treatment of dental caries may influence patients' long-term treatment. The indirect benefit to the patients may be the ultimate improvements in dental treatment in daily clinical practice. The potential benefits to the p-is and indirectly to their patients will far exceed the risk involved with the participation. The p-is will charge their normal fees for the treatment provided.

Subjects will not be paid for their participation. DPBRN p-is will be remunerated \$50 for the first questionable carious lesion per subject enrolled and \$25 for each additional lesion diagnosed on the same patient at the same visit (pending final decision by the DPBRN Executive Committee), after having returned completed forms for 50 questionable carious lesions and after having responded to a possible query from the Regional Coordinator or Coordinating Center to verify illegible or unclear responses.

E.4. Importance of the knowledge to be gained

The knowledge to be gained from the current study will quantify questionable carious lesions. When the results of this study become available, comparisons can be made with responses provided for the Caries Risk Assessment questionnaire.

E.5. Inclusion of women

Both genders will be eligible to enroll. The percentage of practicing dentists in 2003 by gender was 18% female and 82% male (ADA 2003). In Scandinavia the ratio of female: male clinician is about 50:50. Based on the enrollment questionnaires completed by US DPBRN dentists, 14% are females. We anticipate that our targeting of this group during recruitment will yield a sample of 20% female dentists for this study. We anticipate that approximately 55% of the patients enrolled will be female.

E.6. Inclusion of minorities

Racial and ethnic minorities will be included in the study at least proportional to their composition in the dental community. The racial and ethnic distribution of dental practitioners expected to participate in the study is shown in the first Targeted/Planned Enrollment table later in this application. Because minority practitioners and practices that serve high percentages of minority patients will be targeted in Alabama and Florida, we anticipate that approximately 20% of the subjects in this study will be of a racial/ethnic minority group.

E.7. Information to be provided for all clinical research studies

The p-is who participate in this study will be dental practitioners who meet the eligibility criteria previously stated. The patients will be given an explanation of what the study entails and they will also sign an informed consent to participate in regions where such a form is required. No gender or racial/ethnic group will be excluded. Our anticipated enrollment for patients is shown in the Targeted/Planned Enrollment table later in this application.

E.8. Inclusion of children

This study is designed to investigate questionable occlusal carious lesions on a permanent tooth surface by DPBRN p-is. The age of the patients will depend on the dental practice; some p-is restrict their practices to the treatment of adults only, some have 'family type' practices, and some practices treat children and adolescents only. Because recruitment will be limited to permanent teeth, patients will need to have at least one permanent tooth with a questionable lesion to be eligible. This means that subjects will be at least 6 years old because that is when the permanent first molar typically erupts. Parents/guardians of child subjects will provide the informed consent, although study participation also requires the child's assent.

Targeted/Planned Enrollment Table (for the dentist participants)**This report format should NOT be used for data collection from study participants.****Study Title:** Questionable Occlusal Carious Lesions**Total Planned Enrollment:** 75 DPBRN dentists (who treat 2,500 patients) †

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	2	4	6
Not Hispanic or Latino	20	49	69
Ethnic Category: Total of All Subjects *	22	53	75
Racial Categories			
American Indian/Alaska Native	1	1	2
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	6	9
White	19	45	63
Racial Categories: Total of All Subjects *	22	53	75

† We project that the 3,750 lesions diagnosed (75 dentists each doing 50 restorations) will comprise 75 dentists performing treatment on 2,500 different patients.

The gender and racial and ethnic distribution of dental practitioners expected to participate in the study reflects the proportional distribution shown in the Targeted/Planned Enrollment for DPBRN Study 1 and the result of planned Study 2 targeting of dentists who are female and/or of a racial/ethnic minority.

Targeted/Planned Enrollment Table (for the patients participating)**This report format should NOT be used for data collection from study participants.****Study Title:** Reasons for placing the first restoration on permanent tooth surface(s)**Total Planned Enrollment:** 2,500 patients (treated by 75 dentists) †

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	250	100	350
Not Hispanic or Latino	1250	900	2150
Ethnic Category: Total of All Subjects *	1,500	1,000	2,500
Racial Categories			
American Indian/Alaska Native	30	18	48
Asian	50	14	64
Native Hawaiian or Other Pacific Islander	30	18	48
Black or African American	390	250	640
White	1000	700	1700
Racial Categories: Total of All Subjects *	1,500	1,000	2,500

† We project that the 3,750 restorations (75 dentists each diagnosing 50 lesions) will comprise 75 dentists performing treatment on 2,500 different patients.

Because minority practitioners and practices that serve high percentages of minority patients will be targeted in Alabama and Florida, we anticipate that approximately 20% of the subjects in this study will be of a racial/ethnic minority group.

F. VERTEBRATE ANIMALS

N/A

G. LITERATURE CITED

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