Management of Dentin Hypersensitivity

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STATEMENT OF COMPLIANCE

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

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments, and provide 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 United States (US) federal regulations and guidelines.

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A copy of this page is to be signed by all Steering Committee members, Regional Coordinators, and other National Dental Practice-Based Research Network (PBRN) staff members responsible for conducting any portion of the study (if not already designated to sign the protocol above). The signature page should be printed, signed, then scanned into a PDF document and submitted to the Coordinating Center (NDPBRN-helpdesk@westat.com) for storage on the Internal Website.

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, and

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.

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 Manual, Clinical Monitoring Plan, and other applicable plans developed in the future).

Signed: _____ Date: _____

Name: _____

Title: _____

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ANOVA	Analysis of Variance
CC	Coordinating Center
CDM	Clinical Data Manager
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRF	Case Report Form
DH	Dentin Hypersensitivity
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
GEE	General Estimating Equation
GPI	Grant Principal Investigator
HIPAA	Health Insurance Portability and Accountability Act
ICC	Intracluster Correlation
ICF	Informed Consent Form
IRB	Institutional Review Board
LM	Labeled Magnitude
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHRP	Office for Human Research Protections
OTC	Over the Counter
PBRN	Practice-Based Research Network
PD	Protocol Deviation
QA	Quality Assurance
QC	Quality Control
RAS	Regional Administrative Sites
RC	Regional Coordinator
SAE	Serious Adverse Event/Serious Adverse Experience

SOP	Standard Operating Procedures
SPI	Study Principal Investigator
TMJ	Temporo-Mandibular Joint
UAB	University of Alabama at Birmingham
UP	Unanticipated Problem
US	United States
VAS	Visual Analog Scale

PROTOCOL SUMMARY

Title: Management of Dentin Hypersensitivity

Alternate Title: Sensitive Teeth Study

Note*: For easy reference by the participating practitioners and patients, this study will be referred to as the Sensitive Teeth Study on most of the practitioner and patient study documents and communications.*

Précis: This is a prospective, multicenter cohort study of patients with dentin hypersensitivity. For the study, practitioners and patients will be recruited from six National Dental PBRN regions across the US. The study population will consist of adult dental patients (19 years old or older) who have dentin hypersensitivity and the practitioners who provide treatment for this condition. It is anticipated that approximately 180 dentist practitioners across the US will be enrolled (30 practitioners per National Dental PBRN region). Each dental practitioner will be asked to enroll approximately 14 study patients, with an enrollment aim of 2,520 adult patients for the entire network.

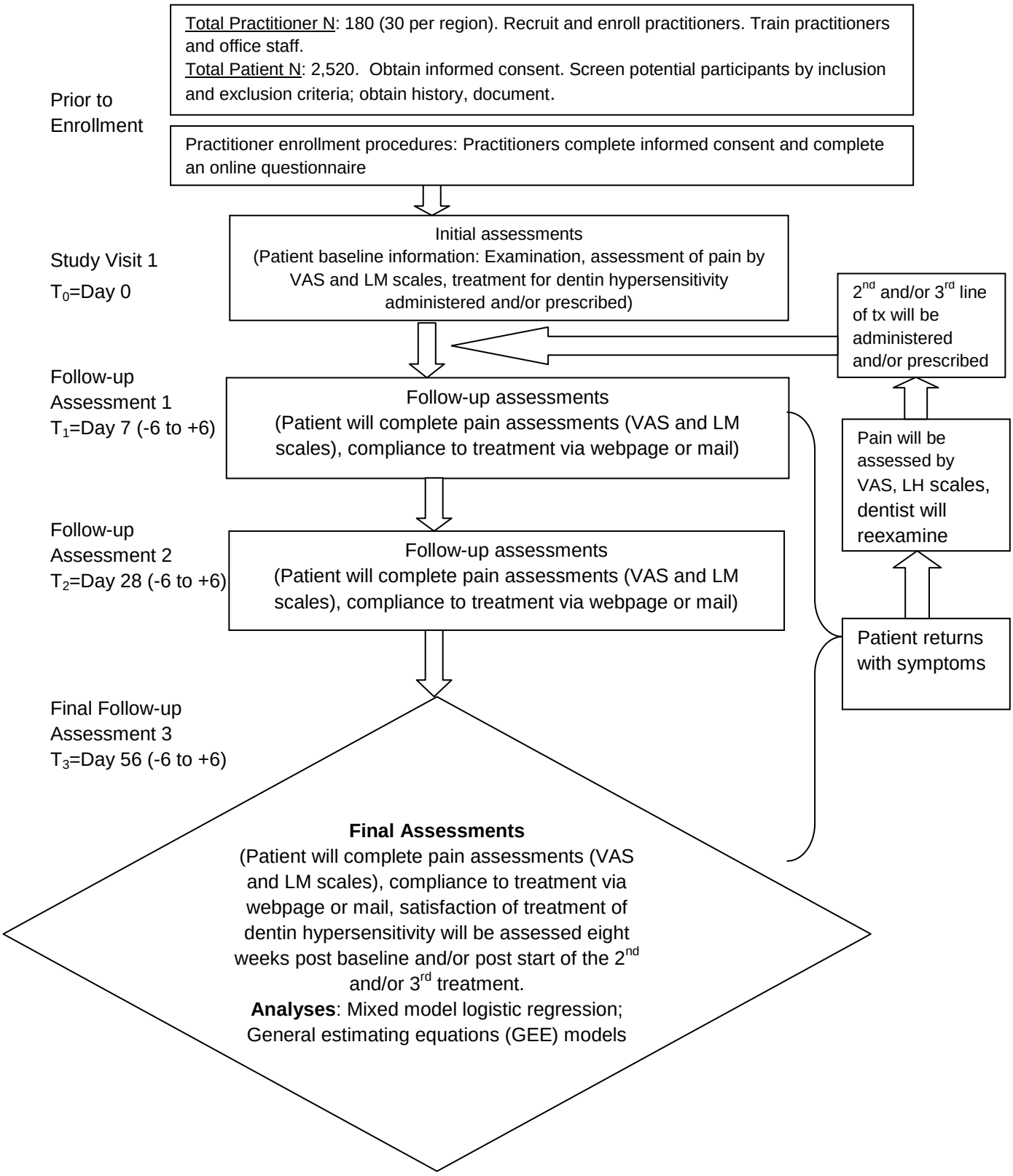
Objectives: **The primary objective** of the study is to gain a better understanding of the multiple treatments used to manage dentin hypersensitivity among US dental practitioners by: characterizing methods of diagnosing dentin hypersensitivity in the practice setting, characterizing dentists' selected treatment(s) of dentin hypersensitivity, and characterizing patient-reported pain outcomes over time**.**

The secondary objectives of the study are to explore patient-, practitioner-, practice- and tooth- level characteristics that may contribute to practitioners' selected treatment(s) and approach(es) to care, and to characterize patients' satisfaction with the received treatment of dentin hypersensitivity.

Primary Outcomes: Data will be gathered on diagnostic methods and treatment modalities that are used for diagnosis and management of dentin hypersensitivity in the practice setting. Patient-reported pain outcomes will be assessed by a reduction in dentin hypersensitivity based on patients' perception of pain assessed by the Visual Analog Scales (VAS) at baseline and at 1 week, 4 weeks and 8 weeks post baseline. Duration, intensity, tolerability and pain description changes will be

	assessed by means of the Labeled Magnitude (LM) scales at baseline and at 1 week, 4 weeks and 8 weeks post baseline. **Secondary Outcomes**: Several patient-, practitioner-, practice- and tooth level characteristics will be collected to explore their relevance to practitioners' selected treatment(s) and approach(es) to care.
Population:	The proposed study will include as subjects approximately 180 dentists and approximately 2,520 adult patients (19 years old or older) from the National Dental PBRN. Patients will represent demographic groups in proportion to the practice population.
Number of Sites:	Approximately 180 National Dental PBRN practices
Study Duration:	24 months
Patient Participation Duration:	Between 8-24 weeks
Estimated Time to Complete Enrollment:	Approximately 2-4 months for practitioners; 4-6 months overall

Schematic of Study Design:



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Dentin hypersensitivity (DH) has been defined as a “short, sharp pain arising from exposed dentin in response to stimuli typically thermal, evaporative, tactile, osmotic or chemical and that cannot be ascribed to any other form of dental defect or pathology”(Canadian Adv, 2003). The stimulus that may trigger the onset of pain can be characterized as being of thermal, chemical or mechanical origin. One of the most frequent patient complaints is related to cold stimuli; pain may also occur when consuming acidic foods (mainly fruit), sweets and salty foods. Mechanical stimulus frequently occurs when the patient brushes his/her teeth or rubs the sensitive area with a finger nail (Porto et al., 2009).

DH is considered to be a relatively common problem encountered in clinical practice. It may disturb patients during eating, drinking and brushing. The prevalence of DH has been reported to be in the range of 8 to 57% in the general population (Amarasena et al., 2010, 2011; Canadian Adv, 2003; Chu et al., 2011; Cummins, 2011; Parolia et al., 2011; Poulsen, 2006; Liu et al., 1998; Gillam et al., 1999; Cunha-Cruz et al., 2013). The diversity of reports could be in part due to different methods used to diagnose this condition and also relying solely on questionnaire data (Dababneh et al., 1999).

For example, among 780 patients that presented to the Health Examination Center of National Taiwan University Hospital, the prevalence of DH was 32% (Liu et al., 1998). The self-reported prevalence of DH among regular attenders in three general dental practices in the United Kingdom was 52%; DH was most prevalent among 30-40 year old patients and it was more common among female patients (Gillam et al., 1999). A cross-sectional study conducted by 19 dental practitioners in the United Kingdom that examined 4,841 patients over a period of one calendar month revealed that 4.1% of patients were diagnosed with DH based on the dentist examination. Upper premolars were the most commonly affected, and cold drinks initiated DH most often. A greater number of sensitive teeth were found in patients with periodontal disease who also smoked (Rees & Addy, 2002).

Data on diagnostic methods used, treatments employed, and perceived success of the treatments were collected in a web survey (December 2008 to June 2009) of Northwest PRECEDENT dentists (n=209; 177 generalists, 32 specialists). Based on the survey, practitioners used a diverse range of methods to identify and characterize DH. The most frequently reported diagnostic method was a spontaneous patient report. Patient reports prompted by a query from the dentist were also common but used less frequently. Practitioners frequently requested a verbal or numeric pain description or asked the patient to rate their pain on a Visual Analog Scale (VAS). The use of a dental explorer or air blast was the most common method of assessing DH clinically (Cuhna-Cruz et al., 2010).c

No clear consensus among Northwest PRECEDENT dentists existed for successfully treating DH, but fluoride varnishes and gels apparently had the most support. Dentists also expressed high levels of interest in testing fluoride varnishes and gels, as well as glutaraldehyde/HEMA and restorative treatments in future studies (Cuhna-Cruz et al., 2010).

DH affects patients of any age with its peak occurrence in middle aged adults. It may affect any tooth, but most often affects canines and first premolars because they are prominent in the arch. It may present clinically on any tooth surface, but most often it occurs on the buccal cervical margins of teeth. Several theories of DH have been proposed. These include hydrodynamic theory, odontoblast transduced mechanism and direct innervation theory (Parolia et al., 2011). None of these mechanisms fully explain this phenomenon. There are a multitude of products that are available for treatment of DH with no conclusive evidence present of reliable and successful treatment regimens, especially in the practice environment.

Based on a cross-sectional survey of 787 adult patients from 37 general dental practices within the Northwest PRECEDENT PBRN that was conducted from September 2010 to May 2011, prevalence of DH was 12.3% (Cunha-Cruz et al., 2013). Patients with hypersensitivity had, on average, 3.5 hypersensitive teeth. The prevalence of DH was higher among patients who were 18-44 years of age and lower among patients who were 65 years of age or older. The prevalence of DH was higher among women and patients with gingival recession and patients who used at home tooth whitening products (Cunha-Cruz et al., 2013).

Although dentin sensitivity appears to be prevalent in adult population groups, no universally used or highly reliable desensitizing agents or treatment modalities have been identified (Holland et al., 1997; Orchardson & Gillam, 2006). Recently the PEARL PBRN conducted a randomized clinical trial, in the practice setting, to assess the outcomes of noncarious cervical lesion treatment choices (Veitz-Keenan et al., 2013). The overall objective of this study was to determine the efficacy of three randomly assigned treatments for hypersensitive noncarious lesions: chemoactive dentifrice use, dentin bonding agent with sealing and flowable resin-based composite restoration. The secondary outcomes were to assess tubule occlusion, retention of resin coating, retention of restoration and change in lesion size. Results of this study suggest that placement of the sealant or resin restoration was effective in reducing hypersensitive noncarious cervical lesions over the six-month study period.

According to the survey of dental practitioners conducted by the Canadian Advisory Board on Dentin Hypersensitivity, approximately 50% of the respondents reported lack of confidence in managing patients' pain due to DH (Canadian Adv, 2003). As suggested by the Canadian Advisory Board on Dentin Hypersensitivity, providers should initiate management of this condition by applying desensitizing treatment that is noninvasive; i.e., desensitizing toothpaste and/or topical agents. Some dental providers use a stepped approach to treatment with multiple visits; others apply and prescribe

multiple treatments at one time. Invasive treatments of DH are also performed by placing a restoration on an otherwise healthy tooth (Canadian Adv, 2003).

2.2 Rationale

The proposed study, which will take place in dental offices across the country that are part of the National Dental PBRN, is optimally located as it brings “real world” settings to the treatment of DH. In this environment, little is known about the products and methods dentists use to treat DH, nor is much known about the effectiveness of these products and treatment modalities. There are various treatment options available to manage DH including conservative and invasive approaches and little is known about their effectiveness.

Given that no universally-accepted guidelines are available to treat DH; this could be the first national study to address this question in the office practice setting. Several techniques have been used to diagnose, treat and manage DH in the practice setting. The ideal desensitizing modality should not irritate the pulp, and should be relatively painless when applied or shortly thereafter, easily applied, fast acting, permanent, and cost effective, and it should not discolor the tooth. A plethora of treatment modalities used for treating DH by dental clinicians suggest that there is no single treatment that may meet the ideal criteria and there is no gold standard for treating DH. Some dental providers use a stepped approach to treatment with multiple visits; others apply and prescribe multiple treatments in a single visit.

By conducting a prospective cohort study, rather than a randomized controlled trial, we can build a picture of how patients with DH are cared for in dental offices in the US and how the practitioner, practice, patient and tooth characteristics relate to the approach to care to provide data for practice guidelines in this domain. This approach has been used effectively in other clinical studies. For example, in a prospective cohort study that evaluated treatment modalities for febrile infants, clinicians did not follow the existing guidelines and used individualized clinical judgment resulting in fewer hospitalizations and unnecessary laboratory testing (Pantell et al., 2004). The proposed study, utilizing data from a sample of National Dental PBRN enrolled dental providers, will improve our knowledge about treatment methods and products that are effective when treating DH and may eventually lead to the establishment of evidence-based guidelines for treating DH.

2.3 Potential Risks and Benefits

This is an observational study. The participants of the study will not receive dental care as a study procedure, but will continue to receive the usual clinical care as patients of the dentists participating in the study. Risks of dental procedures provided as part of usual clinical care are not considered to be study-associated.

2.3.1 Potential Risks

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 of subject information and data. These include use of unique study codes for participants, encryption of data for transmission to the coordinating center, 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.

2.3.2 Potential Benefits

Participation in the study will provide no direct benefit to study participants. Benefits will accrue to society related to better understanding of treatment options of DH and the patient-reported pain outcomes over time. Participation in the study may enhance care for future patients through evidence-based recommendations for more timely and appropriate interventions.

3 OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to gain a better understanding of the multiple treatments used to manage DH among US dental practitioners by:

- Characterizing methods of diagnosing DH in the practice setting,
- Characterizing practitioners' selected treatment(s) of DH, and
- Characterizing patient-reported pain outcomes over time.

3.1.2 Secondary Objectives

The secondary objectives of the study are to:

- Explore patient-, practitioner-, practice- and tooth- level characteristics that may contribute to practitioners' selected treatment(s) and approach(es) to care, and
- Characterize patients' satisfaction with the received treatment of DH.

3.2 Study Outcome Measures

3.2.1 Primary Outcomes

To characterize diagnosis and treatment of DH in the practice setting, practitioners' preferred methods of diagnosing and treating DH will be ascertained via a practitioner

online questionnaire to be completed upon study enrollment and via practitioner data collection forms during patient visits.

Diagnosis of dentin hypersensitivity:

Online practitioner questionnaire: Practitioners' preferred diagnostic procedures that are usually implemented when diagnosing DH in the practice setting will be ascertained. These will include: spontaneous patient report, patient report after dentist's query, applying air blast, applying cold water, scratching dentin with dental explorer, requesting numeric descriptor of pain, requesting visual scale descriptor of pain, and using an electric pulp tester.

Treatment modalities:

Online practitioner questionnaire: Practitioners' preferred method of treatment of DH and the rationale for the elected treatment or treatments will be ascertained. Questions will include preferred treatment modalities (see below) and approach(es) to treatment of DH (i.e., providing multiple treatments at one time, one treatment or staged approach, no treatment, and/or no advice).

Patient visit(s): The usual and customary treatment(s) for DH utilized by the participating practitioner will be applied or prescribed and recorded.

The following groups of treatment modalities will be ascertained:

1. Fluoride products (gels, varnishes, pastes, rinses)
2. Desensitizing over the counter (OTC) Potassium nitrate toothpastes
3. Glutaraldehyde/HEMA products
4. Bonding agents
5. Sealants
6. Restorative treatments
7. Lasers
8. Oxalates
9. No treatment
10. Advice
11. Other

Patient-reported pain outcomes:

Patient visit(s) and follow-up: Patient-reported pain outcomes will be assessed by changes in patient report of pain intensity, duration, and frequency. Patients' perception of pain will be assessed by the Visual Analog Scale (VAS) at baseline, 1 week-, 4 weeks- and 8 weeks- post-baseline. Duration, intensity, tolerability and pain description changes will be assessed by means of the Labeled Magnitude (LM) scales at baseline, 1 week-, 4 weeks- and 8 weeks- post-baseline (Heaton et al., 2013). If patients return

for a second- or third-line of treatment, these pain assessments will be implemented also at 1, 4 and 8 weeks after the initiation of the second- or third-line of treatment.

To the extent possible with the data, pain outcomes will be characterized by patient's predisposing variables that may affect pain reporting, such as age, gender, race/ethnicity, and education level.

3.2.2 Secondary Outcomes

The proposed study will be conducted in six regions of the National Dental PBRN, allowing for a comparison among regions in relation to practitioners' approach(es) to care and treatment of DH based on the patient-, practitioner-, practice- and tooth- level characteristics. To explore the association between the above level characteristics and approach(es) to treatment for DH listed above, several patient-, practitioner-, practice- and tooth- level characteristics will be collected at baseline.

Patient characteristics:

Because this objective will explore characteristics that may contribute to practitioners' selected treatment(s) and approach(es) to care, the practitioner will be asked about the following patient variables at/or soon after the baseline visit:

Patient's predisposing variables: prior periodontal surgery and/or scaling and root planing, recent bleaching history, previous DH episodes and previous/current treatment modalities if any.

Patient's enabling variables: out-of-pocket cost for treatment and/or follow-up appointments after considering dental insurance coverage.

Practitioner characteristics:

The following practitioner variables will be collected upon enrolling in the National Dental PBRN by means of the enrollment questionnaire: age, gender, race/ethnicity, and year of graduation from dental school.

Knowledge about the etiology of DH and predisposing factors related to DH will be ascertained in the practitioner online questionnaire at study enrollment.

Practice characteristics:

The following practice variables will be collected from the practitioner as he/she enrolls in the National Dental PBRN by means of the enrollment questionnaire: practice size, location, practice business, wait time for new patients to be seen, number of patient visits per week, and hours of patient care per week.

Tooth (teeth) characteristics:

The following patient sensitive tooth (teeth) variables will be collected at the baseline visit: number of teeth that are sensitive, tooth (teeth) location, gingival recession, exposed dentin, recent periodontal surgery relating to the sensitive tooth (teeth), number of remaining teeth (surrogate for oral/dental functioning), whether or not the sensitive tooth has a restoration and, if so, the type of restoration, and location and number of surfaces restored.

Patient Satisfaction:

To assess patients' satisfaction with the received treatment for DH, patients' satisfaction with the prescribed treatment modality will be assessed via VAS at 8 weeks post-baseline and will be compared with the treatment rendered. For patients who return for a second- or third-line of treatment, the VAS assessment will be implemented at 8 weeks after the initiation of the last line of treatment.

At each assessment (1-, 4-, and 8- weeks post-baseline), patients will be asked whether or not they complied with the practitioners' treatment recommendation(s).

4 STUDY DESIGN

- This is a prospective, multicenter cohort study of DH. For the study, practitioners and patients will be recruited from six National Dental PBRN regions across the US.
- The study population will consist of adult dental patients (19 years old or older) who have DH and the practitioners who provide treatment for DH. Dental practitioners are included in the population being studied because diagnostic modalities as well as treatment recommendations and approaches for DH are being studied. It is anticipated that approximately 180 dentist practitioners across the US will be enrolled (approximately 30 practitioners per National Dental PBRN region). Each dental practitioner will enroll approximately 14 study patients with an enrollment aim of 2,520 adult patients.
- The prospective, observational, multicenter design of the study will allow us to construct a picture of how patients with DH are cared for in dental offices across the US and how practitioner-, practice-, patient- and tooth- characteristics relate to the selected treatment(s) and approach(es) to care. The proposed study will provide further understanding about DH management based on a sample of US dental providers enrolled in the network and may provide data to establish guidelines for treating DH. The usual and customary treatment of DH that dentists apply in their practice will be assessed.
- After enrolling in the study and providing consent, practitioners will receive a link to a secure webpage and will be asked to complete an online questionnaire before recruiting and enrolling patients to the study.
- To determine if a patient meets the criteria for study inclusion, the patient must first indicate intraoral pain/sensitivity by self-report. Patients with a medical condition that could interfere with reliable pain reporting (e.g., cognitive impairment, dementia), chronic pain condition (fibromyalgia, lower back pain, irritable bowel syndrome, temporo-mandibular joint (TMJ) disorder), and patients who report having taken analgesics more than three times in the past week will be excluded from the study. Next, the practitioner will perform an oral examination to assess other causes of tooth sensitivity such as pulpitis or dental infection. A diagnosis of DH will be made when the practitioner has excluded other etiologies of odontogenic pain.

- Study patients will complete baseline assessments in dental offices and then will complete follow-up assessments 1-, 4- and 8-weeks post-baseline visit via an online or mailed questionnaire to record patient-reported pain outcomes. Patients who do not have a reduction of symptoms after the first-line treatment may return to the participating dentist due to continued discomfort and/or dentists' recommendation for a second-line treatment. If this occurs within 8 weeks of the initial treatment, study procedures (VAS, LM scales, and clinical exam) will be repeated for the second-line treatment administered or prescribed. The same process will apply if a third-line treatment is administered or prescribed. For patients who receive second- or third- line treatment, follow-up assessments will be obtained via online or mailed questionnaire at 1-, 4- and 8- weeks after the initiation of the second- or third-line of treatment, and follow-up assessments from the previously administered or prescribed treatment will no longer be warranted. Patients will be followed until approximately 8 weeks after the last administered treatment of DH, if it occurs within 8 weeks of the initial treatment. Patients' participation in the study will be 8 to 24 weeks as presented in the study flow diagram (page xi).
- It is anticipated that each practitioner will be able to enroll approximately 14 patients in 2-4 months. It is expected that the study will be fully-enrolled in approximately 6 months.
- The study duration for patients will be at minimum 8 weeks, to include in-office treatment for DH followed by follow-up assessments via online or mailed questionnaire at 1-, 4- and 8- weeks after treatment. Patients who return for second- or third-line treatments during the initial 8-week period due to pain and/or dentist's recommendation will be followed through 8 weeks after the last administered and/or prescribed treatment (maximum study length for patients is approximately 24 weeks).
- The Study Team will pilot test the practitioner online questionnaire with up approximately six practitioners to assess it in terms of length and acceptability. The Study Team will refine the questionnaire based on practitioner feedback and administer the revised questionnaire to 24 additional practitioners to quantify and document test-retest reliability. The website will be assessed for acceptability and Internet browser compatibility of the electronic questionnaire prior to administration with study participants.
- The same team (as above) of six practitioners enrolled in the study will be asked to pilot the data collection process, including online questionnaires and patient assessments, and modifications will be made as appropriate or necessary. During this phase, each practitioner will enroll approximately five patients in the study. These practitioners along with the 24 test-retest practitioners may continue to enroll patients (approximately 14 patients) unless there are changes to the critical data elements of the study as a result of the pilot. The pilot data will be included in the final analysis of the data unless certain data elements change as a result of the pilot.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, a practitioner must meet the following criteria:

- Any National Dental PBRN practitioner (i.e., general dentist and specialist) who is enrolled in the network at the full participation level.
- Practitioner affirms that the practice will devote sufficient time to allow for all of the study procedures.

The subject population for the study will be derived from the National Dental PBRN practices participating in the study. The expected sample for the study will include approximately180 practitioners, each enrolling approximately 14 patients presenting with DH, for a total sample size of 2,520 patients.

In order to be eligible to participate in this study, a potential study patient must meet all of the following criteria:

- Agrees to participate in the study and complete the informed consent requirements according to the National Dental PBRN region approvals.
- Willing to comply with all study procedures and be available for the duration of the study.
- Age ≥ 19 years.
- Reports having a sensitive tooth or teeth (3rd molars will be excluded) diagnosed with DH*.
- Has access to a phone, and agrees to receive text messages, emails, or phone calls related to the study. (The patient's preferred method of contact will be ascertained).
- Willing to be contacted on a regular basis by each of these entities: the practice, Regional Coordinator (RC), and the Westat Coordinating Center (CC).
- Willing to provide contact information of one person living at a different address who will know the patient's whereabouts in the event the patient cannot be reached.

* A diagnosis of DH will be based on the following from the patients' history and clinical examination: a) Patient's self-report of tooth pain, and b) Practitioner's exclusion of other dental and periodontal conditions that may be etiologies of tooth pain. Conditions

that need to be ruled out when diagnosing DH are listed in the exclusion criteria below. DH will be therefore a diagnosis of exclusion (Holland et al., 1997).

5.2 Subject Exclusion Criteria

A patient who meets any of the following criteria will be excluded from participation in this study:

- Has a medical condition that could interfere with reliable pain reporting (e.g., cognitive impairment, dementia).
- Has a chronic pain condition (fibromyalgia, lower back pain, irritable bowel syndrome, TMJ disorder).
- Has odontogenic pain (pain due to pulpitis, dental infection).
- Reports having taken analgesics (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics) more than three times in the past week.

5.3 Strategies for Recruitment and Retention

5.3.1 Practitioner Recruitment

We have estimated that we need to enroll approximately180 practitioners to participate in this study; approximately 30 practitioners per National Dental PBRN region. This is based on the targeted enrollment of approximately 2,520 patients presenting with a sensitive tooth or teeth. All National Dental PBRN practitioners will be eligible to be approached for participation in this study. The practitioners will be asked for their interest in participating in the study. If more than 180 practitioners would like to participate in the study, practitioners will be selected systematically to provide a representative sample. The first priority will be to select practitioners on the basis of geographic region, with the aim of enrolling 30 practitioners per National Dental PBRN region. If there will be more than 180 practitioners and more than 30 practitioners from the National Dental PBRN region who would like to participate in the study, additional selection criteria will be used in the following significance: type of practice (solo practitioner, small group practice, large group practice, community dental practice), location (urban, suburban, rural), practitioner's experience (number of years in practice), practitioner's gender, race/ethnicity and age to obtain a representative cohort of practitioners. The RCs from the six regional administrative sites (RAS) will assist in recruitment of the practitioners to the study. RCs have a positive and close rapport with the network enrollees. Practitioners will be compensated for their time allocated to the study. Practitioners will receive $50 for completing the online study questionnaire and $25 for each patient office visit.

5.3.2 Patient Recruitment

We plan to enroll approximately 2,520 patients in an approximate 4-6-month period. Each practitioner will be asked to recruit approximately 14 patients. Recent data from

the Northwest PRECEDENT network have shown that the prevalence of DH among the patients seen by the practitioners enrolled in the previous network was 12.3% (Cunha-Cruz et al., 2013).

Any dental or hygiene visit will be eligible for patient recruitment to the study. A convenience sampling approach will be used to enroll patients in the study with an emphasis upon enrolling the first 14 patients presenting to the dental office who meet the eligibility criteria.

Patients presenting with DH at any dental visit in the dental office will be eligible for the study. Designated office personnel will introduce the study to patients who meet the inclusion criteria when they are seen for a dental appointment. Patients who meet eligibility criteria and show interest in participating in the study will be invited to participate, and a designated person will perform informed consent procedures. It is anticipated that in most instances it will be a dentist who will perform informed consent procedures. Patients will receive $125 for their participation - $25 upon completion of the baseline office visit, $25 upon completion of the follow-up assessment at 1 week, $25 upon completion of the follow-up assessment at 4 weeks and $50 upon completion of the study.

5.3.3 Patient Retention

Patient retention is important to this study and follow-up data will be collected independently of in-office visits. The subject retention plan is presented in Appendix B. Study patients will be asked to complete follow-up assessments on a designated webpage 1-, 4-, and 8- weeks after the baseline visit. According to the US census data, it is estimated that about 70% of US households have computers with Internet access. Patients who do not have access to the computer with Internet will return the study documents by mailing them to the designated RC 1-, 4- and 8- weeks post-baseline. A designated office person will provide study documents with instructions to patients who would like to return study data collection forms via US mail. Patients who return for second- or third-line treatments during the initial 8-week period will be followed for an additional 8 weeks after the last administered/prescribed treatment in the same manner.

Based on patients' preferences, study patients will be contacted via a text message system or phone message to their designated phone number or will receive an email prior to each follow-up interval (1-, 4-, and 8- weeks after the baseline visit) and will be asked to complete the appropriate assessment. Two to three contact attempts per assessment will be implemented.

The RCs, with the assistance from the CC, will follow up with patients who do not complete the web-based or mail surveys by the due date to encourage them to complete study procedures.

5.4 Subject Withdrawal

5.4.1 Reasons for Withdrawal

Practitioners and patients are free to withdraw from participation in the study at any time upon request.

5.4.2 Handling of Patient Withdrawals

In the case of patient withdrawal from the study, staff will only attempt continued follow-up data collection for patients who are withdrawn due to an unanticipated problem (UP). In these circumstances, only data related to the completion of reporting requirements for the UP will be recorded. For patients withdrawn from the study for any other reason, the date and reason for withdraw will be recorded and no additional study data will be collected. Patients withdrawn from the study may continue to receive usual dental care as patients of the participating dentists, however, additional study data will not be collected from continuation of the usual clinical care (except as noted above).

Replacement of patients who withdraw or discontinue early will be allowed, but only during the initial 2-4-month patient enrollment period for each practitioner. The practitioner may attempt to enroll one replacement patient for each patient enrolled who withdraws or discontinues during the practitioner-specific enrollment period.

5.5 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 SPI 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.
- Determination of futility.

6 STUDY SCHEDULE

The practitioners enrolled in the National Dental PBRN who express interest in the study will be invited to participate. Study information and instructions will be provided by regional staff to interested practitioners. 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 Binder will carefully describe the subject selection procedures,

methods for approaching subjects and obtaining Informed Consent, methods for data collection, and other study procedures. A summary flow chart will be sent to the practices with a description of the enrollment and baseline visits 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 RCs will be in close contact with practitioners prior to the study initiation to ensure that the practitioner and his/her office staff are familiar with study procedures.

The study will proceed in the following stages:

1) Each region will enroll approximately 30 practices into the study;

2) Practice personnel will receive any necessary IRB training prior to starting the study;

3) Practitioner informed consent process (if required by that region's IRB), Individual Investigator Agreements, University of Alabama at Birmingham (UAB) Master Service Agreement, and similar documents will be obtained prior to the start of the study;

4) Practitioners will complete the online practitioner questionnaire;

5) RCs will ensure practices are trained in the appropriate study procedures (see below); and

6) Practitioners will screen and enroll eligible study patients into the study.

The CC along with the RAS and RCs will coordinate the launch of the study. After the participating practitioner has undergone informed consent procedures and has completed the online practitioner questionnaire, and when the practice has been trained by the RC in appropriate study procedures, the practice would be ready to recruit patients into the study. It is desirable that within each practice, the patient enrollment is performed in a 2-4-month period, so that the practice can maintain its focus on data collection for this study. The enrollment period will be based on number of eligible patients seen per month by the practitioner. The entire enrollment period will take approximately 4-6 months to complete for six regions.

6.1 Practitioner Enrollment/Baseline

- Obtain and document consent from practitioner participant according to regional IRB requirements.
- Verify practitioner inclusion/exclusion criteria.

- Obtain practitioner online questionnaire data.

6.2 Patient Screening

A prospective study patient may be recruited at any dental appointment in the dental office participating in the study. A patient who indicates oral pain by self-report and meets the inclusion criteria may be eligible for participation in the study. Assessment of study inclusion will involve: a) Reviewing medical conditions and medication usage specified as study exclusion criteria, b) Performing an oral examination to rule-out oral conditions that warrant study exclusion, and c) Confirming a diagnosis of DH. A diagnosis of DH will be based on the following from the patients' history and clinical examination: 1) Patient's self-report of tooth pain, and 2) Practitioner's exclusion of other dental and periodontal conditions that may be etiologies of tooth pain. Conditions that need to be ruled out when diagnosing dentin hypersensitivity are listed in the exclusion criteria in Section 5.2. If study inclusion criteria are met, and a patient expresses interest in the study, the designated office staff will introduce the study to the patient. Enrollment and baseline study procedures will occur at the same dental visit at which eligibility is confirmed.

The procedures listed below are consistent with those included in the Schedule of Events (Appendix A).

6.3 Enrollment/Baseline

Patients who agree to participate in the study and meet the inclusion criteria will be enrolled in the study. The regionally-approved consent process will be completed by a designated office staff member, most likely the dentist.

If an eligible patient declines participation in the study, this occurrence will be noted in the patient log and the informed consent process will not be completed; it will be considered as failure to provide informed consent.

Enrollment/Baseline Visit (Visit 1, Day 0, time of this visit is denoted by t_{1_0})

- Obtain and document consent from patient according to regional IRB requirements.
- Verify inclusion/exclusion criteria.
- Obtain patient contact information and preferred method of contact.
- Obtain patient demographic data.
- Obtain patient self-reported pain assessments.
- Record results of dental examinations related to DH.
- Record treatment recommendations and treatment administered/prescribed.

6.4 Intermediate Follow-up Assessments

The data will be completed by patients online on the designated webpage or by completing a printed questionnaire and mailing it to the designated RCs.

Follow-up Assessment 1, Day 7 (-6 days to +6 days) (t_{1_1})

- Patients will complete pain assessment/compliance to treatment questionnaire.

Follow-up Assessment 2, Day 28 (-6 days to +6 days) (t_{1_2})

- Patients will complete pain assessment/compliance to treatment questionnaire.

6.5 Final Follow-up Assessment

Final Follow-up Assessment 3, Day 56 (-6 days to +6 days) (t_{1_3})

Patients will complete pain assessment/compliance/satisfaction with treatment questionnaire.

6.6 Study Visits for Patients Returning for Additional Treatment

- Patients who do not have a reduction of symptoms after the first-line treatment may return to the participating dentist for a second-line treatment due to continued discomfort and/or dentist's recommendation if the dentist routinely utilizes a "stepped approach" to DH management. If this occurs within 8 weeks of the initial treatment, study procedures (VAS, pain intensity, clinical exam) will be repeated for each second-line and third-line treatment that is administered or prescribed.

- Recommended (by dentist) and actual (when appointment occurs) time interval(s) between treatment(s) will also be recorded. Patients will be contacted via text message system, phone or email 1-, 4- and 8-weeks post-additional treatment and will be followed until 8 weeks after the last administered DH treatment.

6.6.1 Second-Line Treatment Visit

Second-Line Treatment Visit (t_{2_0}) may occur between 1-56 days ($1 \geq t_{2\_0} \leq 56$) since the baseline visit at t_{1_0}:

- Obtain patient self-reported pain assessments.
- Record results of dental examinations.
- Record treatment recommendations and treatment administered/prescribed.

Follow-up Assessment 1, Day 7 + t_{2_0} (-6 days to +6 days) (t_{2_1})

- Patients will complete pain assessment/compliance to treatment questionnaire.

Follow-up Assessment 2, Day 28 + t_{2_0} (-6 days to +6 days) (t_{2_2})

- Patients will complete pain assessment/compliance to treatment questionnaire.

Final Follow-up Assessment 3, Day 56 + t_{2_0} (-6 days to +6 days) (t_{2_3})

- Patients will complete pain assessment/compliance/satisfaction with treatment questionnaire.

6.6.2 Third-Line Treatment Visit

Third-Line Treatment Visit (t_{3_0}) may occur between 1-56 days ($1 \geq t_{3\_0} \leq 56$) since the second-line treatment visit at t_{2_0}:

- Obtain pain assessments.
- Record results of dental examinations.
- Record treatment recommendations.

Follow-up Assessment 1, Day 7 + t_{3_0} (-6 days to +6 days) (t_{3_1})

- Patients will complete pain assessment/compliance to treatment questionnaire.

Follow-up Assessment 2, Day 28 + t_{3_0} (-6 days to +6 days) (t_{3_2})

- Patients will complete pain assessment/compliance to treatment questionnaire.

Final Follow-up Assessment 3, Day 56 + t_{3_0} (-6 days to +6 days) (t_{3_3})

- Patients will complete pain assessment/compliance/satisfaction with treatment questionnaire.

6.7 Withdrawal Visit

- Record date and reason for withdrawal.
- Obtain pain assessment and treatment compliance/satisfaction information only if withdrawal occurs during an in-office visit, if consent was not withdrawn.

7 STUDY PROCEDURES/EVALUATIONS

7.1 Study Procedures and Evaluations

After entry into the study, a patient will undergo a baseline visit that will involve visual inspection of the oral cavity and further evaluation of the most sensitive tooth/teeth identified by the patient. Data regarding the duration and impact of symptoms, pain frequency and intensity, types and number of teeth affected, and DH treatment will be recorded.

Patients who return to the dental office within 8 weeks after the baseline visit due to continued discomfort on the tooth/teeth that received initial treatment and/or dentists' recommendation will be re-examined by the practitioner as described above. If the diagnosis has not changed, any second-line treatment for DH that is implemented and/or prescribed will be recorded. If patients return to the dental office within 8 weeks after the second-line treatment visit due to continued discomfort and/or dentists' recommendation, another re-examination will occur as described above, and any third-line treatment that may be implemented/and or prescribed will be recorded. The patient pain assessment is completed at the office visit after re-examination (see Subsection 7.2 below), and follow-up pain assessments via online or mailed questionnaire will occur through 8 weeks after the second/third-line treatment visit(s).

7.2 Questionnaire Administration

Prior to enrolling study patients, participating practitioners will complete an online practitioner questionnaire that will ascertain modalities used to diagnose DH as well as treatment modalities and approaches towards treatment of DH (see Section 3.2).

Practitioners will be asked about their patients' predisposing and enabling variables at/ or soon after the baseline visit (see Section 3.2.2).

At the baseline visit after the oral examination, patients will complete a pain assessment questionnaire that will ascertain the pain intensity, frequency, and duration. Patients will record pain levels by using LM pain scales that were developed at the University of Washington specifically to assess the pain associated with DH (Heaton et al., 2013). These four 100-millimeter (mm) horizontal scales are labeled with descriptive terms to assess the intensity, duration, tolerability and description of the participant's pain experience. Patients will also complete a standard 100-mm horizontal VAS on which the endpoints are marked "not painful" and "most intense pain sensation imaginable."

The clinical symptom of DH is likely associated with the "overall patient experience" because there is likely spatial summation. When an individual drinks cold fluids, for example, his/her DH/pain would be associated with multiple teeth (if multiple teeth are sensitive). Rating each tooth could only be achieved if the dentist systematically isolated each tooth and stimulated each one separately -- which doesn't mimic the clinical condition. The VAS/LM ratings will be applied to assess the overall patient pain experience associated with DH. The LM pain scales capture specific dimensions of pain that characterize the DH pain response (Heaton et al., 2013).

At 1-, 4- and 8- weeks post-baseline and/or second/third-line treatment visit(s), pain intensity, frequency, and duration will be re-ascertained as described above to measure patient-reported pain outcomes via an online or mailed questionnaire. Compliance with treatment will also be assessed via one Likert-like question. Treatment satisfaction will be assessed by one VAS question 8-weeks post the last treatment visit.

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 (SAE).

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

An 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.

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 (AE), 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 AE, incident, experience, or outcome;
- An explanation of the basis for determining that the AE, incident, experience, or outcome represents an unanticipated problem; and
- 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 SAEs 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 1 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

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 Grant PI's (GPI) and Study PI's (SPI) responsibility for oversight, study oversight will be under the direction of the PBRN 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.

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 the NIDCR. The NIDCR reserves the right to conduct independent audits as necessary.

11 STATISTICAL CONSIDERATIONS

The study is characterized by an estimation- rather than hypothesis-driven approach. The aims of identification and quantification of dentists' selected treatment(s) for DH and methods selected for the diagnosis of DH in the practice setting will be addressed by estimation of percentages of dentists using each method and percentages of patients for which each method was used, and calculation of confidence intervals (CIs) to evaluate the precision of each estimate.

11.1 Sample Size Considerations

The expected sample for the study will include approximately 180 practitioners, each enrolling 14 patients presenting with DH, for a total sample size of approximately 2,520 patients.

Calculations of sample size requirements for the primary objectives addressing estimation of percentages were based on widths of 95% confidence intervals for binomial proportions, adjusted for the effect of clustered sampling, with clusters defined by sampling multiple patients within the same dental practice. Adjustment for clustering was done by calculating effective sample sizes using variance inflation factors for a range of likely values of intracluster correlation (ICC). Power to detect a difference between proportions of dentists using each of the treatment modalities were estimated for chi-square tests, adjusted for the effect of clustered sampling in order to approximate the power of the proposed GEE analysis.

Sample size requirements for the primary objective of characterizing the trajectories of patient-reported pain outcomes over the study period, and for comparing these changes among the different treatments selected by the practitioners, were based on the expected widths of 95% CIs for the percentages of use of each of the treatments and diagnostic methods, and secondarily on t tests for comparisons of changes in VAS scores between two treatments, adjusted for the effect of clustering and for multiple treatment comparisons, again in order to approximate the power of the proposed GEE analysis. Power was calculated for comparison of two groups because the actual number of treatments observed will not be known until after the data is collected. In the absence of information on group size, the sample was assumed to be equally divided. Power was calculated for the conventional "medium effect size", represented by a between-group difference in means equal to one-half of the within-group standard deviation. Additionally, the difference in means that would be detectable with 80% power was calculated, and expressed as a multiple of the within-group standard deviation. Expected CI widths were based on the Normal approximation to the binomial distribution, and were calculated around 50% in order to provide conservative estimation. Precision of estimation of mean change in pain scores was calculated based on the widths of 95% CIs for change in reported pain scores, also using the expected mean numbers of subjects in equal-sized treatment groups. These CIs are expressed in standard deviation units.

The actual analysis will compare all the treatment groups that occur in the study, using an analysis of variance approach which will incorporate the entire sample. While the groups will be smaller than in this approximation, this will be somewhat offset by incorporating the entire sample in calculation of the standard error, so that power will be greater than would be calculated using only a portion of the patients in separate pairwise comparisons of treatment groups.

The nQuery Advisor version 7.0 software package was used to calculate expected confidence interval widths and power estimates.

Outcome measure used for calculations

The outcome measures that were used for sample size calculations for tabulation of treatment and diagnostic method use were the treatment techniques listed by the dentists and the diagnostic techniques, as presented in the dentist surveys. The sample size calculations for these are identical, but the number of treatment techniques is not known in advance, while we will know the number of diagnostic techniques that will be included. Patients' rating of DH using VAS responses were used as the outcome variable for evaluation of patient-reported pain outcomes over time.

Test statistic

Power for hypothesis testing was based on t tests and chi-square tests. Precision of estimation of percentages was based on widths of 95% confidence intervals for the binomial distribution. Precision of estimation of mean change in pain scores was based on widths of 95% confidence intervals for the normal distribution.

For the primary objective, study precision calculations were based on widths of 95% confidence intervals, rather than on power of hypothesis tests.

Type I error rate

The Type I error rate will be set at 5% for all analyses.

Type II error rate

The target Type II error rate is 20%, corresponding to statistical power equal to 80%. Power was calculated for a range of effect sizes, yielding ranges of power estimates.

Method for adjusting calculations for planned interim analyses, if any

No interim analyses are planned.

Assumptions used in calculations

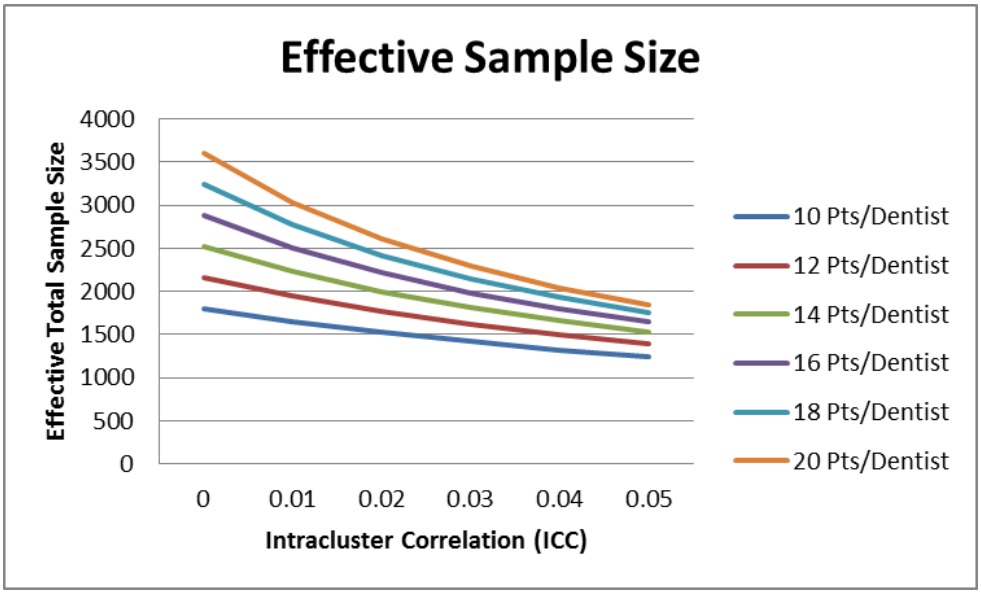
Confidence interval width and power estimation for percentages of the dichotomous outcomes use of treatment modality and use of diagnostic techniques were based on

event rates of 50%, yielding the most conservative estimates by providing the widest estimated confidence interval width and a lower bound on power. This approach was used in order to somewhat offset possible inflation of power estimates due to approximation of equivalence of adjusted chi-square and t tests to the proposed GEE analysis, or to other errors of assumption in the calculations.

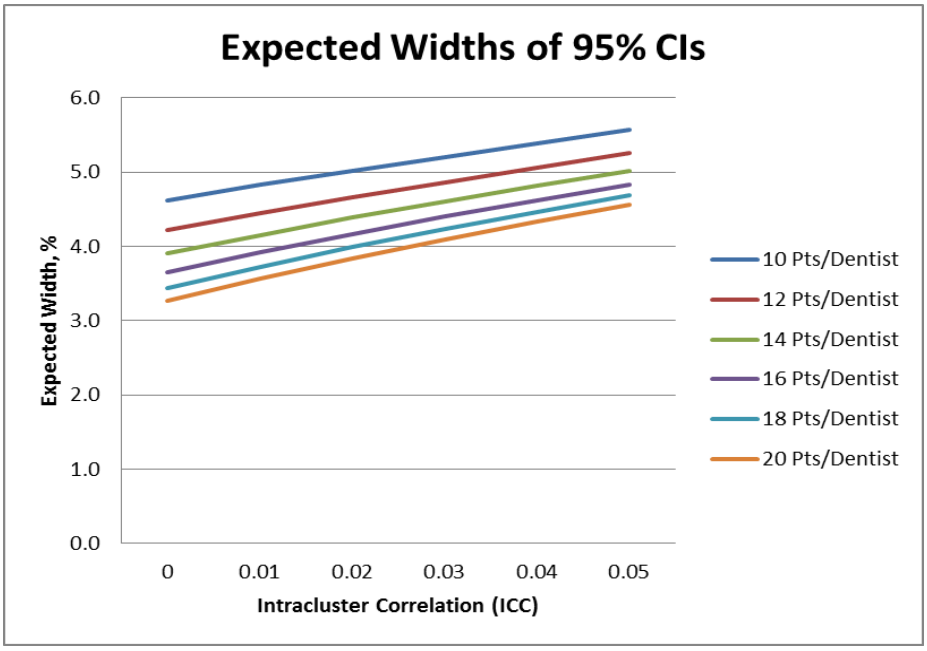
Data for objectives 1 and 2 are collected cross-sectionally, at a single patient visit. Thus, withdrawals are not anticipated for these analyses. For objective 3, loss to follow-up is a possibility. All available data for each patient will be used in the GEE analysis models. Least-squares adjusted means will be calculated in order to avoid biasing main effects means due to missing values.

Present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size. Most assumptions are not accurate as point estimates.

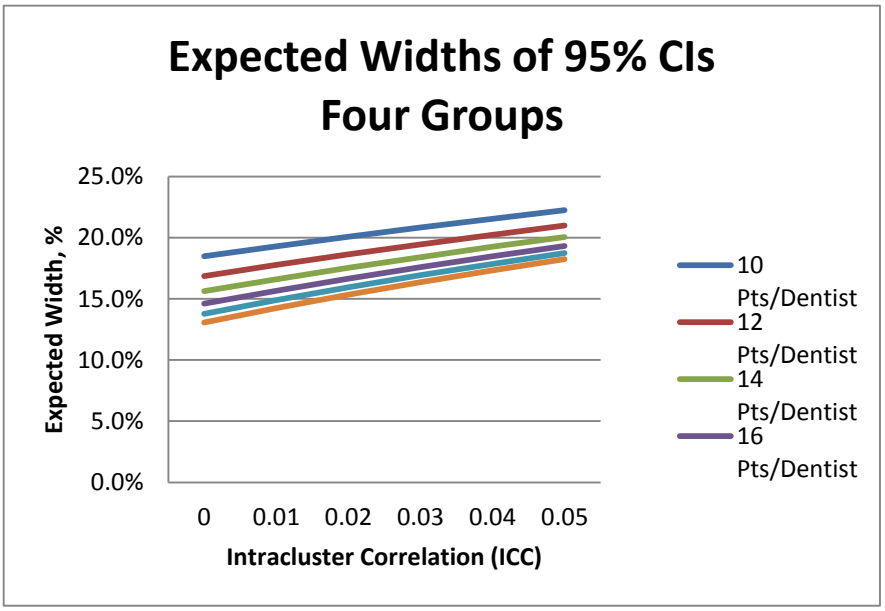
Effective sample sizes were calculated for 180 dentists, 10 to 20 patients per dentist, and values of ICC from 0.00 to 0.05. Expected widths of 95% confidence intervals around a true proportion of 0.50 were calculated for each effective sample size. The value of 0.50 was used as this is the value that yields the maximum variance for a binomial distribution, for a given sample size. Thus, these calculations provide upper bounds for the widths of confidence intervals for each sample size, providing conservative estimates in case ICC is higher than expected. Effective total sample sizes for the different values of ICC and numbers of patients per dentist are presented in the following chart.



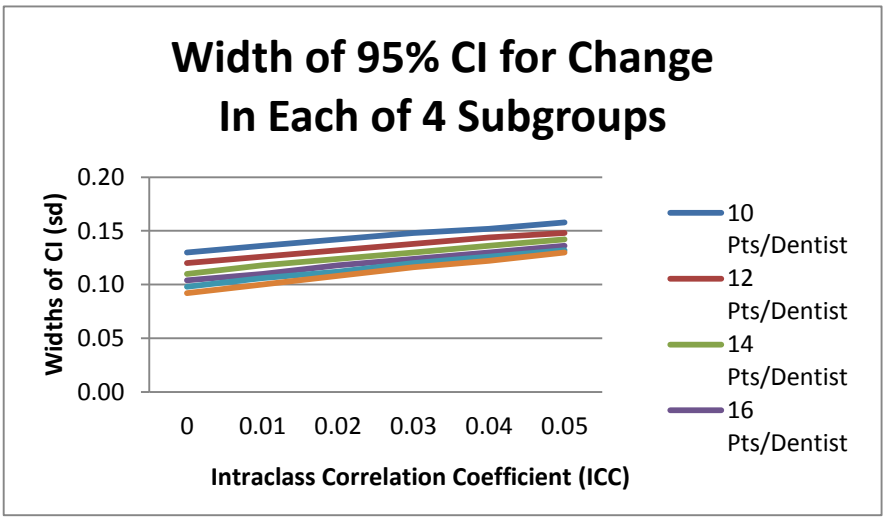
The expected widths of confidence intervals for the primary estimation aims are presented in the following chart. The first set of expected widths was calculated for the entire sample, to illustrate the total information content of the sample, given each of the sample size choices. These expected widths range from 3.3%, reflecting estimation within ±1.65%, for 20 patients per dentist and ICC equal to 0.0, to 5.0%, reflecting estimation within ±2.5%, for 10 patients per dentist and ICC equal to 0.05. As seen in the plot, increasing the number of patients per dentist from 10 to roughly 16 provides substantial increases in precision, with smaller gains in precision with increases to 18 or 20 patients per dentist.



Assuming that four main treatment groups occur, then the expected widths of 95% CIs on the percentages of patients in each of these subgroups would range from 13.1% (estimation within ± 6.5%) for 20 patients per dentist and ICC equal to 0.0 to 22.3% (estimation within ± 11.15%) for 10 patients per dentist and ICC equal to 0.05. The expected widths of these CIs are shown in the following chart, which presents the same pattern across sample sizes as that for the entire sample.

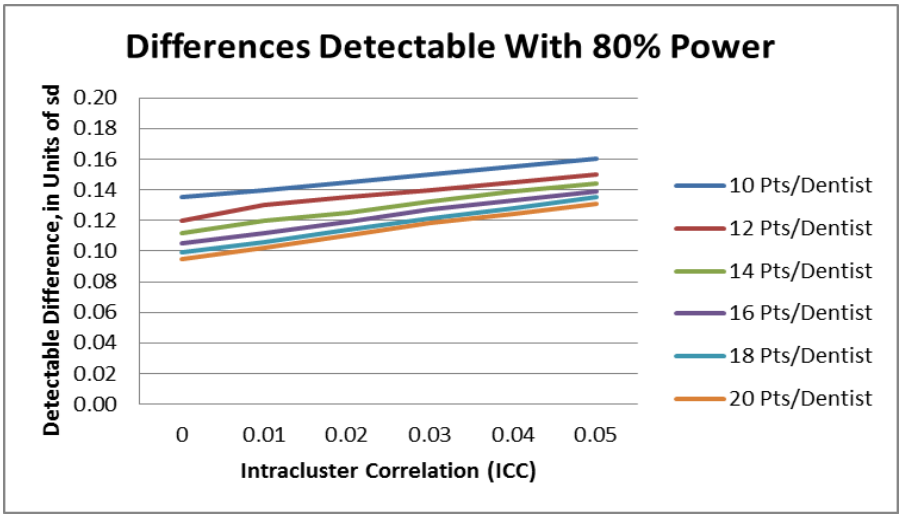


Precision of estimation of mean change in reported pain scores is shown in the following chart. Four equal-sized subgroups of the total sample were assumed. Widths were calculated for CIs within a single subgroup. Precision is represented as the widths of 95% confidence intervals, based on the Normal distribution, in units of standard deviation of the change scores.

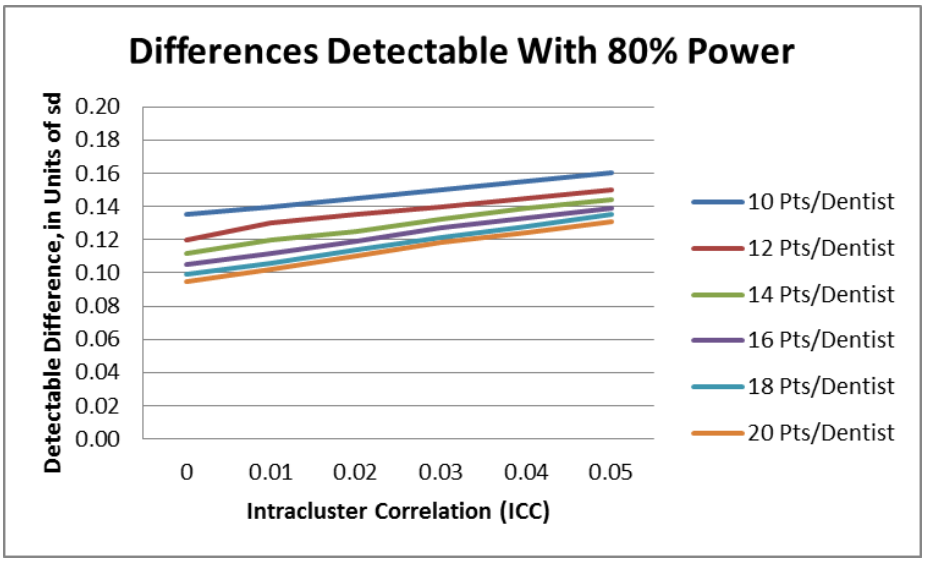


Power to detect a medium effect size for difference in VAS score between treatments is approximately 100% for all effective sample sizes that were considered. Differences between group means that would be detectable range from 0.095sd for 20 patients per dentist and ICC equal to 0.0 to 0.160sd for 10 patients per dentist and ICC equal to 0.05. Thus, all configurations that were considered provide substantial power to detect very small effect sizes, yielding confidence that the study will be adequately powered,

even if ICC is larger than those assumed in the power calculations. Power to detect a difference between treatment group means is shown in the following chart.



Given the results of these power calculations and practical considerations, we will recruit 180 dentists, who will each recruit 14 patients, for a total sample size of 2,520 patients. This will provide protection against loss of power due to potential dropout of patients or of dentists, and against finding larger than expected correlation among observations made by the same dentists. If a patient loss to follow-up of 20% were to occur, the study would still include 2,016 patients, which would still provide essentially 100% power to detect a medium effect size, for likely magnitudes of ICC. Similarly, while it is unlikely that practitioner dropout will occur, loss of as many as 10 practitioners would result in a total expected sample size of 2,380 patients, again providing very high power if ICC is of the expected magnitude. The proposed sample size provides substantial protection against the possibilities that ICC might be higher than anticipated or that the effect size might be smaller than anticipated.



11.2 Final Analysis Plan

Analysis plan for Primary Objectives:

#1. To characterize methods of diagnosing DH in the practice setting.

(This will done by asking questions by means of an online questionnaire on what practitioners usually do when diagnosing DH.)

Practitioners' responses to questionnaire items will be summarized and reported as frequencies and percentages. Ninety five percent confidence intervals will be calculated for percentages. The primary analytic approach for this Aim will not be based on hypothesis testing.

#2. To characterize dentists' selected treatment(s) of DH.

Analysis approach: This descriptive aim will be addressed by tabulating the treatment modalities used by practitioners during the study. Percentages of practitioners using each modality and percentages of total patients who received each modality will be calculated. Confidence intervals for percentages of patients receiving each of the treatment modalities will be calculated, with adjustment for clustering by dentist. Comparisons of percentages among the treatment modalities will be conducted using a mixed model logistic regression, to account for the effect of correlation due to obtaining multiple observations from each practitioner. A term representing the individual practitioner will be specified as a random effect in the analytic model, and estimation will be implemented using GEE. An indicator variable representing treatment modality will be included as a fixed effect.

#3. To characterize patient-reported pain outcomes over time.

Analysis approach: Patients' ratings of dentin sensitivity will be compared across the observation times using generalized linear models. Terms representing individual practitioners and patients will be included as random effects in the analytic model, to account for correlation among multiple patients per practitioner and multiple observation times per patient. Terms representing observation time and treatment modality will be included as fixed effects. The statistical test that will be of primary interest will be the time by treatment interaction term, which would reflect different trajectories of reported pain levels among the treatment modalities. This analysis model will also provide group-specific means and standard errors, accounting for clustering, which will allow estimation of trajectories of pain outcomes across time. Plots of adjusted means across time will be constructed for each of the subgroups in the analysis, along with appropriate measures of variability. It should be noted that the measures of change within individual treatment groups do not separate change due to treatment from that due to natural time course or other causes. Comparisons of means between treatment groups do reflect the differences between treatment effects because the effects of causes that are common to both groups are removed in the calculation of the differences.

Depending on the nature of the distribution of the reported VAS scores, this analysis will be implemented either as a general linear mixed-model, if the residual distribution is approximately normal, or a generalized mixed-model, if a non-normal distribution is required. Other approaches that may be considered for the analysis of non-normal measures include using data transformations or analysis of ranked data.

Analysis plan for Secondary Objectives:

#1. To explore patient-, practice- and tooth- level characteristics that may contribute to practitioners' selected treatment(s) and approach(es) to care.

Analysis approach: Occurrence of patient-reported symptoms, predisposing factors and other patient-level variables, and practitioner-reported restoration-level and practice-level variables will be compared among the treatment modalities using a mixed-model multiple logistic regression approach. A term representing the individual practitioner will be specified as a random effect in the analytic model, and GEE estimation will be utilized in order to account for the clustering effect of multiple patients for each practitioner. Analyses will be conducted using each of the treatment modalities as the dependent variable. Potential predictor variables will be evaluated for association with the use of each treatment modality.

#2. To characterize patients' satisfaction with the received treatment of DH.

Analysis approach: Patients' reported satisfaction scores will be compared among the treatment modalities using mixed-model analysis of variance (ANOVA), accounting for correlated observations within practitioner. The specific implementation of the mixed-model ANOVA, as a normal-theory general linear model or a generalized linear model for non-normal data, will be based on the sample distribution of the scale scores. The statistical test that will be of primary interest will be the test for a main effect of treatment modality. Multiple comparisons will be conducted using Tukey's adjustment for multiple comparisons.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate 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 (QA) 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 case report forms (CRFs): clinical and office charts 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: Baseline Exam, Symptomatic Exam, Patient History, all Pain Assessments, and 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 Health Insurance Portability and Accountability Act (HIPAA) regulations. These records will be subject to examination and copying as stated elsewhere in this section.

13 QUALITY CONTROL AND QUALITY ASSURANCE

For the QA/quality control (QC) activities associated with data collection and processing, the CC will develop a data management plan in which the specific data QA/QC procedures will be provided. 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 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 in the study protocol. The RCs will perform QA review of a percentage of CRFs, as specified in the data management plan. In these QA reviews, data entered into the web-based system will be compared against CRFs. Mismatches will be corrected in the web system. 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 is complete and the data are verified and approved for accuracy, the database will be locked for final analysis. Although no interim analysis is planned, if interim data analysis is needed during the study period, 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 C.

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

The protocol, consent form(s), recruitment materials and all participant materials will be submitted to the regional IRBs for review and approval. 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.

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

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. If required by the responsible IRB, 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. The timing for the signing of the consent form required by the responsible IRB will be adhered to if written consent is required (i.e., before or after other study procedures). 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 informed 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.

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

Participating practices will designate the individual(s) who will execute informed consent for the study. In most cases this will be the dentist practitioner(s). Any personnel who will be assigned to perform consent procedures will be defined as study personnel and will complete required IRB training. Consent procedures will be performed in the participating practice prior to enrolling a patient into the study.

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

Children 19 years of age and older will be included in this study. Only permanent teeth are of interest to ensure that enrolled teeth can remain for the duration of the study.

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.

Practitioners and patients will be assigned unique identification numbers, which will be used to maintain study records and organize data transcripts. A file linking practitioners' and patients' names with their unique identification number will be kept in a password-protected file on the CC's computer, separate from all other research records.

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 (e.g., office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

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 Data Management Plan is detailed in Appendix D.

Only study personnel (i.e., GPI, SPI, Co-Investigator's, RCs, and 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 from practitioners, perform a QC review and send the forms to the CC for data entry into the online web system. For the paper CRFs that are to be used as source documents (see Section 12), the RAS staff will ensure the signatures on the forms are completed and the copies are securely stored at practitioners' sites. The RAS staff and the CC 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 and/or patients 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 paper CRF completion and electronic data entry guidelines. All of the paper CRFs will be sent to the CC for data entry by CC staff.

15.2 Data Capture Methods

Study-specific paper CRFs will be developed to include fields for all data elements required for participant assessments. A secure webpage will also be developed and used to capture data from an online practitioner questionnaire as well as patient follow-up assessments for those who choose to complete them online. A Web-based data collection system will ensure that all required data (paper and online) are collected in the study database. As most fields will require a categorical response and some fields will ask for a numeric response, the data field 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 at enrollment and follow-up by the practitioners and patients will be made available on the network web site.

After the paper data collection has been completed for a participant at enrollment and at each follow-up assessment, the study materials for the participant will be placed in a secure location. The participant log will be consulted to obtain the name of the patient corresponding to the study ID number printed on the CRF. Questions about the data will be resolved by conferring with the staff member(s) or the patient who completed the CRF. After the dentist signs the CRF, the designated staff member will transmit the data to the RCs. The trained staff at the RAS will review the data and send it to the CC for data entry into the study database. RAS staff members will respond to data queries generated by the data capture system and will have access to support staff at the CC if they need assistance with data processing.

Patients will be responsible for the submission of the 1-, 4-, and 8-week follow-up assessments within the study assessment windows. Reminders and other tools will be used to encourage timely submission of these assessments however it is known that some patients may not comply. Follow-up assessments received outside of the study specified windows will be accepted; though this data may not be included in the analysis, it would still be of interest to the study team.

15.3 Types of Data

Data for the present study consist of the following:

- Practitioner-level data from the National Dental PBRN enrollment questionnaire and the study online practitioner questionnaire,
- Patient characteristics data from baseline questionnaire,
- Patient-, pain-, treatment compliance-, and satisfaction follow-up assessments, and
- Unanticipated problems data (collected in the main study database).

15.4 Schedule and Content of Reports

Reports to monitor enrollment will be produced every 2 weeks during the 4-6-month participant enrollment period, until enrollment targets are attained and enrollment is closed. These reports will contain a section for accrual information in aggregate, with information on accrual of participants according to key characteristics (symptomatic vs. asymptomatic) cross-tabulated with treatment recommendation (Yes vs. No). These reports 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. In addition to enrollment and retention reporting, the DSMB study progress reports will contain safety data as well as frequencies and

descriptive statistics for primary outcome variables and key variables. The identification of key variables will be determined by the SPI and other study team members.

Reports to assess study retention will be produced every 2 weeks. These reports will provide ongoing monitoring of participant retention. Retention data will be closely monitored, and futility analyses will be performed as needed. In addition, a report will be produced for each individual practice that includes the practice's attrition rate and a comparison to the overall attrition rate for the study. These reports will be made available to the practitioners. For patients who are lost to follow-up, reports to assess reasons for loss will be produced after data has been obtained following the data collection period for each study follow-up assessment.

The procedure for locking the database prior to final analysis will be detailed in Section 13 of the study Data Management Plan, in accordance with the Westat CCs *SOP DSD-001: Development of a Data Management Plan* (see Appendix D) and *SOP DSD-405: Data Lock*. Briefly, the 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 National Institutes of Health (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.

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 (PD) is any noncompliance with the clinical study protocol or 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 PD that is reportable to an IRB must also be reported to NIDCR. NIDCR defers to the IRB for reporting time-frame requirements. Once a PD 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 PDs to their IRB, that reporting frequency is acceptable to NIDCR. At the time of each DSMB review, all previously unreported PDs 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

1. Amarasena, N., Spencer, J., Ou, Y., & Brennan, D. (2010). Dentine hypersensitivity - Australian dentists' perspective. Australian Dental Journal, 55(2), 181-187.

2. Amarasena, N., Spencer, J., Ou, Y., & Brennan, D. (2011). Dentine hypersensitivity in a private practice subject population in Australia. Journal of Oral Rehabilitation, 38(1), 52-60.

3. Canadian Advisory Board on Dentin Hypersensitivity. (2003). Consensus-based recommendations for the diagnosis and management of dentin hypersensitivity. Journal of Canadian Dental Association, 69(4), 221-226.

4. Chu, C. H., Lam, A., & Lo, E. C. (2011). Dentin hypersensitivity and its management. General Dentistry, 59(2), 115-22; quiz 123-4.

5. Cummins, D. (2011). Advances in the clinical management of dentin hypersensitivity: A review of recent evidence for the efficacy of dentifrices in providing instant and lasting relief. The Journal of Clinical Dentistry, 22(4), 100-107.

6. Cunha-Cruz, J., Wataha, J. C., Heaton, L. J., Rothen, M., Sobieraj, M., Scott, J., et al. (2013). The prevalence of dentin hypersensitivity in general dental practices in the Northwest United States. Journal of the American Dental Association (1939), 144(3), 288-296.

7. Cunha-Cruz, J., Wataha, J. C., Zhou, L., Manning, W., Trantow, M., Bettendorf, M. M., et al. (2010). Treating dentin hypersensitivity: Therapeutic choices made by dentists of the northwest PRECEDENT network. Journal of the American Dental Association (1939), 141(9), 1097-1105.

8. Dababneh, R. H., Khouri, A. T., & Addy, M. (1999). Dentine hypersensitivity - an enigma? A review of terminology, mechanisms, aetiology and management. British Dental Journal, 187(11), 606-11; discussion 603.

9. Gillam, D. G., Seo, H. S., Bulman, J. S., & Newman, H. N. (1999). Perceptions of dentine hypersensitivity in a general practice population. Journal of Oral Rehabilitation, 26(9), 710-714.

10. Heaton, L. J., Barlow, A. P., & Coldwell, S. E. (2013). Development of labeled magnitude scales for the assessment of pain of dentin hypersensitivity. Journal of Orofacial Pain, 27(1), 72-81.

11. Holland, G. R., Narhi, M. N., Addy, M., Gangarosa, L., & Orchardson, R. (1997). Guidelines for the design and conduct of clinical trials on dentine hypersensitivity. Journal of Clinical Periodontology, 24(11), 808-813.

12. Liu, H. C., Lan, W. H., & Hsieh, C. C. (1998). Prevalence and distribution of cervical dentin hypersensitivity in a population in Taipei, Taiwan. Journal of Endodontics, 24(1), 45-47.

13. Orchardson, R., & Gillam, D. G. (2006). Managing dentin hypersensitivity. Journal of the American Dental Association (1939), 137(7), 990-8; quiz 1028-9.

14. Pantell, R. H., Newman, T. B., Bernzweig, J., Bergman, D. A., Takayama, J. I., Segal, M., et al. (2004). Management and outcomes of care of fever in early infancy. The Journal of the American Medical Association, 291(10), 1203-1212.

15. Parolia, A., Kundabala, M., & Mohan, M. (2011). Management of dentinal hypersensitivity: A review. Journal of the California Dental Association, 39(3), 167-179.

16. Porto, I. C., Andrade, A. K., & Montes, M. A. (2009). Diagnosis and treatment of dentinal hypersensitivity. Journal of Oral Science, 51(3), 323-332.

17. Poulsen, S., Errboe, M., Lescay Mevil, Y., & Glenny, A. M. (2006). Potassium containing toothpastes for dentine hypersensitivity. Cochrane Database of Systematic Reviews (Online), (3) (3), CD001476.

18. Rees, J. S., & Addy, M. (2002). A cross-sectional study of dentine hypersensitivity. Journal of Clinical Periodontology, 29(11), 997-1003.

19. Veitz-Keenan A, Barna JA, Strober B, Matthews AG, Collie D, Vena D, Curro FA, Thompson VP., Treatments for hypersensitive noncarious cervical lesions: a Practitioners Engaged in Applied Research and Learning (PEARL) Network randomized clinical effectiveness study. *The Journal of the American Dental Association (May 1, 2013) 144, 495-506*

APPENDICES

Appendix A: Schedule of Events

	Baseline Study Visit				2nd-Line Treatment Visit				3rd-Line Treatment Visit				
Procedures	Enrollment/Baseline (Day 0)	1 Wk Follow-up (Day 7, -6 to +6)	4 Wk Follow-up (Day 28, -6 to +6)	8 Wk Follow-up (Day 56, -6 to +6)	2nd-Line Treatment	1 Wk Follow-up (Day 7, -6 to +6)	4 Wk Follow-up (Day 28, -6 to +6)	8 Wk Follow-up (Day 56, -6 to +6)	3rd-Line Treatment	1 Wk Follow-up (Day 7, -6 to +6)	4 Wk Follow-up (Day 28, -6 to +6)	8 Wk Follow-up (Day 56, -6 to +6)	Premature Discontinuation/ Withdrawal
Obtain Informed Consent	X												
Assessment of Eligibility Criteria	X												
Review of Medical/Dental History	X												
Obtain/confirm contact information and preferred method of contact	X				X				X				
Oral Examination	X				X				X				
Patient Demographics (in office)	X												
Pain Assessment (in office)	X				X				X				X[1]
Treatment prescribed and/or performed	X				X				X				
Follow-up Pain Assessment (online or mail)		X	X	X		X	X	X		X	X	X	
Compliance with treatment		X	X	X		X	X	X		X	X	X	X[1]
Satisfaction with treatment				X				X				X	X[1]

[1] Obtain only if withdrawal occurs during an in-office visit and consent is not withdrawn.

Appendix B: Subject Retention Plan

This Subject Retention Plan provides an outline of the matters related to the retention of the study subjects and the procedures for maximizing subject retention during the course of the study.

Minimizing attrition of the study subjects in the study "Management of Dentin Hypersensitivity" is a paramount necessity. High retention rate of the study subjects increases the validity and generalizability of the obtained data by ensuring that missing data due to incomplete follow-up assessments of the study subjects does not affect study findings.

Retention of study subjects is a multifaceted problem. Difficulties with maintaining complete follow-up can be due to a variety of causes. It is important to identify and delineate the different types of retention issues because the way to address them will depend on their type. The four types of retention matters are:

Lost: Subjects move and their new location cannot be found.

Missing Data: Subjects remain within the practice but follow-up assessment is missed.

Refused: Study subjects decide that they do not want to continue participating in the study.

Unable: Subjects are no longer seeing their original/enrolling practitioner.

Below the National Dental PBRN describes the plans for addressing each of these retention matters. Also provided are other administrative and design methods that will help to increase subject retention rates.

Methods to Minimize "**Lost**"

1) At subject enrollment, emphasize study requirements to subjects:
   a. Study subjects are part of a longitudinal study (time in the study: 8 to 24 weeks), and the importance of post baseline visit assessments.
   b. RCs or the CC will contact subjects by telephone to arrange subject completion of the post-treatment questionnaire even if they change dentists.
   c. Entry criteria will include the ability and likelihood of maintaining participation throughout the study.
   d. Collect information on:
      i. Home address
      ii. Home telephone number

iii. Cell phone number
iv. Email address(es)
v. Contact information (including cellular telephone and email) of one person who does not live in the same household as the subject and who will know of the subject's whereabouts.

2) At the end of baseline visit, confirm contact information (of subject and the one contact person).

3) Make contact with study subjects prior to the follow-up assessment due date. The subject's preferred method of contact (e.g., text message, email, or telephone) will be ascertained at the baseline appointment.

4) Prior PBRN studies have shown that personal relationships, both between the subjects and offices, and the offices and the RCs promoted successful execution of PBRN studies. It will be important to study subjects to receive a message from the RCs or CC regarding a reminder for a study follow-up assessment.

5) Experience from the prior network has also shown that it is important to relieve burden on the practices. As such, the National Dental PBRN will request IRB approval for the RCs and for the CC to receive the subject contact information and the contact information of one person who does not live in the same household as the subject, to assist the RCs and the CC in their follow-up with the study subjects post baseline. The regions will have some latitude in determining the best means for maintaining contact with the study subjects and ensuring their ongoing participation.

6) Number of Subjects per Practitioner Considerations:
Ask practitioners to enroll at least approximately 10-14 subjects during the enrollment period.

7) Given the above design features, subjects should not be "lost". However, if a subject moves and contact is lost, the CC has extensive experience with using tracing resources such as National Change of Address services, motor vehicle departments, and LexisNexis databases. In those cases, the CC may implement those tracking procedures.

8) The process for contacting subjects for follow-up assessments will be attempted by the RC and the CC. If unsuccessful, the CC may initiate tracking procedures to identify updated subject contact information. Initiating tracking procedures promptly when there is no subject response to contact attempts will minimize missed follow-up assessments and also minimize loss to follow-up.

Methods to Minimize "**Missing Data**"

1) Put all participating practitioners on the same study schedule. Have an enrollment phase, then a break, then another specific follow-up phase of a couple of weeks and continue this cycle over the course of the study. Offices in general do a good job enrolling subjects because they are focused on the study every day during the enrollment period. However, it is more challenging to remember to perform study procedures when the enrollment phase is over and they may only have a study subject in the office once every couple of weeks. Within the enrollment period, the office enrolls eligible subjects, with a goal of 10-14 subjects. Subjects will be required to complete their follow-up assessments at 1-, 4- and 8-weeks post baseline visit. Prior to each assessment interval, subjects will be contacted via text message, email or phone to remind them about the upcoming assessment. The method of the preferred contact will be ascertained at the baseline visit. The CC and RCs will be responsible for making these reminders. Subjects will return the study assessments by completing them on the designated webpage or mailing them by the US post office to the designated RC.

2) Ask participating offices to develop a system to flag records of subjects in their practices who are participating as subjects in the study, as well as to flag study subjects in the office schedule. In this way, study personnel will be alerted to the fact that the subject is at the office, and can ensure that data collection takes place if indicated. Flagging the subject in the schedule will help to ensure that subjects are not inadvertently scheduled when the practitioner will not be in the office. In the same way, if a subject's record is requested by another office, study personnel can inform the RC and attempts made to maintain the subject in the study.

3) For subjects returning with symptoms, ask the practitioners to set aside specific time for follow-up in the office as necessary or appropriate.

4) Emphasize to practitioners as part of their initial study packages that the dentist has to be the motivational director of the study, especially regarding explaining to the study subjects that follow-up assessments are essential components of the study and make sure that the staff understands that the office is committed to taking the study on and seeing it through to completion.

Methods to Minimize "**Refused**"

1) The method described under Methods to Minimize "Lost", first point, will also help reduce the number of subjects who refuse to continue participating. At enrollment, subjects are informed that they are agreeing/consenting to participate in a longitudinal study. Subjects who enroll are required to state a willingness to participate throughout the study.

2) The method described under Methods to Minimize "Lost", third point (making contact prior the follow-up assessment interval), should also help reduce refusals. Additionally, follow-up involvement will be kept as light and convenient for the subject as possible.

Methods to Minimize "**Unable**"

1) There are several scenarios in which a subject stops seeing the original/enrolling practitioner:
   a. Subject does not move, but:
      i. Subject changes dentists- in same practice
      ii. Subject changes dentists- in different practice
      iii. Subject stops seeing any dentist
   b. Subject moves
      i. Subject sees new dentist
      ii. Subject stops seeing any dentist
   c. Dentist retires or dies
   d. Dentist moves
   e. Dentist refuses to continue participating (shouldn't happen)

2) The operational impact of all of the above scenarios can be summarized by two scenarios:
   a. Subject has a new dentist (not a National Dental PBRN member)
   b. Subject stops seeing any dentist

3) Locating the subject should not be a problem (see Methods to Minimize "Lost"), and having the subject agree to continue participating should not be a problem (see Methods to Minimize "Refused").

4) The main operational issue is: How to get study follow-up assessment information from subjects seeing a non-National Dental PBRN dentist or not seeing any dentist.
   a. Actively recruit the new dentist into the Network so the subject can continue to be followed by the new dentist.
   b. Request permission from the new office to complete a chart abstraction to obtain data.

Appendix C: Quality Management Plan

This Study Quality Management Plan organizes the plans for QA/QC across the Management of Dentin Hypersensitivity Protocol study timeline and study activities. Some of the planned QA/QC activities are described in the main text of the protocol. Specifically, the QA/QC for Data Collection and Management is described in Section 13. The Subject Retention Plan in Appendix B is also a key component of QA/QC of subject follow-up assessments. The Data Management Plan described in Appendix D 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 ensure that they understand the expectations of them for the study and ensure 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 and study personnel at the practitioners' locations by the RC on the protocol and procedures as outlined in the study MOP is a planned QA activity. This will ensure 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 ensure 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.
    c. 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 and follow-up.

3. **Subject Follow-up:**
    a. The QA/QC activity described under 2b above will be continued until all subject follow-up is complete.
    b. Further QA/QC of subject follow-up is described in the Subject Retention Plan in Appendix B.
4. **Data Collection:**
    a. The Study Manager will perform a QC review of the data collected on the first patient enrolled by each practitioner after the enrollment visit and provide feedback to the RC, practitioner, and practice. This early QC is a key component of ensuring 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 Section 13 and Appendix D.
5. **Data Analysis and interpretation:**
    a. All data analyses for presentations and publications will be verified by a "secondary" programmer/statistician to ensure the 1) validity of statistical programming to correspondence with interpretation, and 2) appropriate analytic results (output) are correctly presented in presentation and/or publication.
6. **Manuscript Writing, conference presentations:**

    a. The National Dental PBRN has a Publications and Presentations policy. The SPI will ensure that this policy is followed for any manuscripts and conference presentations. This policy ensures the quality of all National Dental PBRN manuscripts and presentations through the requirement of specific QC 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 and Presentations Committee.

Appendix D: Data Management Plan

The Management of Dentin Hypersensitivity Study CC 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:

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