

# **Predicting Outcomes of Root Canal Treatment**

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## **STATEMENT OF COMPLIANCE**

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

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## SIGNATURE PAGE

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

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## LIST OF ABBREVIATIONS

AAE	American Association of Endodontists
AE	Adverse Event/Adverse Experience
CC	Coordinating Center
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DMP	Data Management Plan
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
FFR	Federal Financial Report
FWA	Federal Wide Assurance
HP IDCC	HealthPartners Institute Data Coordinating Center
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IRB	Institutional Review Board
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
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PBRN	Practice-Based Research Network
PD	Protocol Deviations
QA	Quality Assurance
QC	Quality Control
RAS	Regional Administrative Site
RCT	Root Canal Treatment
SAE	Serious Adverse Event/Serious Adverse Experience

SD                    Source Documents  
SOP                  Standard Operating Procedure  
SPI                   Study Principal Investigator

## PROTOCOL SUMMARY

**Title:** Predicting Outcomes of Root Canal Treatment

**Précis:** Severe post-operative pain following root canal therapy (RCT) occurs in about 20% of patients. The presence of persistent pain following RCT is about 10%, and initial evidence suggests that half of these patients experiencing persistent pain have a non-odontogenic etiology for this pain. Applying odontogenic strategies to treat non-odontogenic pain may increase incidence and duration of chronic oral pain. The overarching goal of this prospective observational cohort study is to investigate risk factors for severe pain following RCT, the prevalence and impact of persistent pain following RCT, and the impact of severe and persistent pain on health-related quality of life. Patient and treatment-related data will be collected before and after RCT completion. Follow-up data will be collected 1 week, 6 months, and 12 months following RCT completion. Approximately 175 practitioners from six National Dental PBRN regions will enroll approximately 2,000 adult patients.

**Objectives:**

*The objectives of this study include:*

**Objective 1 (primary):** Develop a predictive model for severe post-operative pain experienced during the 7 days following completion of RCT, using pre- and intra-operative patient-and procedure-related factors

Objective 1 outcomes will be a set of patient-, disease-, and procedure-related factors that may be associated with severe post-operative pain intensity ( $\geq 7$  on scale 0-10).

**Objective 2 (secondary):** Assess the proportion of patients reporting odontogenic and non-odontogenic persistent pain at 6 and 12 months following RCT completion, and the impact of persistent pain on functional status and health-related quality of life at 12 months following RCT completion

Objective 2 outcomes include: 1) patient-reported persistent pain ( $\geq 1$  on intensity scale 0-10 plus  $\geq 1$  days of pain over the last 30 days) at 6- and 12-month follow-up; 2) practitioner assessment of odontogenic or non-odontogenic pain at 12 months; 3) radiographic evidence of healing at 12 months; 4) estimates of

self-reported temporomandibular and persistent dentoalveolar pain status at 6- and 12-months; and 5) jaw functional status and overall health-related quality of life at 12-months following RCT completion.

- Population:** Approximately 2,000 adult patients age  $\geq 18$  years, except in Nebraska where consent is age  $\geq 19$  years, who underwent RCT treatment within practices of participants in the National Dental Practice Based Research Network (National Dental PBRN).
- Number of Sites:** Approximately 175 (~115 general dentists and ~60 endodontists) National Dental PBRN practitioners
- Study Duration:** Approximately 3 years
- Subject Participation Duration:** Approximately 15 months for patients and approximately 19 months for practitioners
- Estimated Time to Complete Enrollment:** Practitioner Enrollment = approximately 6 months  
Patient Enrollment = each practitioner will have approximately 10-14 weeks to enroll patients; overall study enrollment = approximately 6 months

## Schematic of Study Design

### Practitioner Enrollment & Follow-up

N = Approximately 175 participating National Dental PBRN **practitioners** undergo informed consent, per regional IRB requirements. RCs train practitioners and their staff/personnel.

### Study Visit (SV) 1 Patient Enrollment SV1= Day 0

N = Enroll 2,000 patients in need of RCT:  
For patients willing to be screened, **practitioners or staff** assess study inclusion and exclusion criteria, explains requirements. Eligible **patient** undergoes informed consent, per regional IRB requirements, and is enrolled in the study

### Study Visit (SV) 1a Baseline (treatment initiation) SV1= Day 0

N ~ 1,600 patients (~80%) with 1 RCT appointment:  
**1a. Patient** completes Patient Contact Form, Patient Before Treatment and After Treatment Questionnaires  
**1a. Practitioner** completes Practitioner Before Treatment Questionnaire

N ~ 400 patients (~20%) with ≥2 RCT appointments:  
**1a. Patient** completes Patient Contact Form, Patient Before and After Treatment Questionnaires  
**1a. Practitioner** completes Practitioner Before Treatment Questionnaire

RCT treatment

### Study Visit (SV) 1b Treatment completion SV1b= Day n

**1b. Practitioner** completes After Treatment Questionnaire, uploads periapical radiograph(s)

Interim visits – no data collected

**1b. Practitioner** completes After Treatment Questionnaire, uploads periapical radiograph(s)

### 1-Wk Follow-up (SV2) SV2=SV1b+7 to 14 Data Analysis 1 (DA1) for SV1-SV2 data

**Patient** completes the Patient 1-Week Questionnaire at 7 (+7) days post treatment completion (SV1b day), electronically or by phone

### 6-Mo Follow-up (SV3) SV3=SV1b+180 to 210 DA2 for SV1-SV3 data

**Patient** completes the Patient 6-Month Questionnaire at 180 (+30) days after completion of RCT (SV1b day), electronically or by telephone

### 12-Mo Follow-up (SV4) SV4=SV1b+365(305 to 455) DA3 for SV1-SV4 data

**Patient** completes the Patient 12-Month Questionnaire and receives a clinical evaluation by the treating practitioner at 365 (-60 to +90) days after completion of RCT  
**Practitioner** completes the Practitioner 12-Month Questionnaire and uploads periapical radiograph(s), if indicated for clinical care at 365 (-60 to +90) days after completion of RCT

Submit final study dataset

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# 1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 1.1 Background Information

Previous National Dental PBRN research found nearly 20% of RCT patients reported severe post-operative pain (Law et al. 2015) and 10% reported persistent pain at 6 months following RCT (Nixdorf et al. 2016). These findings suggest that pain following RCT is more prevalent than previously reported in the literature, with prior accepted estimates of 8.4% for severe post-operative pain (Tsesis et al. 2008) and 5.3% for persistent pain (Nixdorf et al. 2010b). Persistent pain following RCT is known to degrade physical functioning and quality of life (Durham and Nixdorf 2014, Shueb et al. 2015) and persistent pain following other surgical procedures is believed to occur through a severe post-operative pain pathway (Katz and Seltzer 2009).

Previous research investigating predictive factors for severe post-operative pain following RCT is well summarized in Cohen's Pathways of the Pulp (Keiser and Byrne 2006). They present 12 predictors from 38 studies that include presenting factors (*i.e.*, patient- and tooth-specific factors, diagnoses) and procedural factors (*i.e.*, retreatment, intracanal medicament, apical patency, one-step versus multiple appointments). However, this body of literature is subject to major limitations due to: 1) design problems (*e.g.*, retrospective), 2) small sample sizes, 3) important predictors not included (*e.g.*, psychosocial variables), 4) difficulty interpreting outcome measures (*e.g.*, composite of pain and office visit), or 5) inadequate control for bias in the analyses (*e.g.*, only bivariate). Because of these limitations, it is difficult to draw clear conclusions, which limits the ability to develop predictive models. Assessment of our data from Study 17 (conducted during the previous funding cycle) suggested that self-report of stress level, pain interfering with daily activities, maxillary tooth location, and a diagnosis of symptomatic apical periodontitis were significant independent predictors of severe post-operative pain when age, gender, geographic region, and specialist status were included in the model (Law et al. 2015).

Nixdorf et al. (2010b) and Vena et al. (2014) found that 3.4% and 3.1% of patients, respectively, reported having persistent pain at 6 months that could not be attributed to a local odontogenic etiology, *i.e.*, non-odontogenic pain. Nixdorf and colleagues (2016) found that among a sample of patients reporting persistent pain at 6 months, 42% had exclusively non-odontogenic pain, 37% had exclusively odontogenic pain, and 11% had both odontogenic and non-odontogenic pain, while 11% were pain-free (Nixdorf et al. 2015). The 53% of patients reporting non-odontogenic pain was similar to rates reported in systematic reviews (Nixdorf et al. 2010a). Most patients with non-odontogenic pain have been diagnosed with TMD (Nixdorf et al. 2015). While this recent research was prospective in nature using a sample patient population that seemed to represent the

typical American patient receiving RCT, the subset used to explore reasons for the persistent pain was small and derived from one geographic region of the country.

The impact of acute pain associated with odontogenic disease has been explored using measures of oral health quality of life (Dugas et al. 2002, Petricevic et al. 2009, Shueb et al. 2015) and this research suggests that those suffering from this pain experience significant impairment. Days of lost productivity in the week prior to receiving RCT for acute pain associated with odontogenic disease has also been explored (Law et al. 2014) and RCT has been shown to reduce this impairment, much like RCT has been shown to improve components of oral health quality of life (Dugas et al. 2002). While this is helpful in understanding the impact of acute pain associated with odontogenic disease and its treatment, these results do not address the domains recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT (Dworkin et al. 2005); (*i.e.*, jaw function, psychosocial factors) or more global measures, such as general quality of life that would be needed to allow for comparison with other disease states and their treatments. Some data exists regarding acute pain, but little is known about persistent pain following RCT. One study assessed oral health quality of life in patients 3 to 5 years following RCT, but these investigators have yet to report the impairment associated with persistent pain compared to those without persistent pain (Vena et al. 2014). Another study observed that patients with persistent pain 6 months following RCT on average experienced mild-to-moderate pain intensity, about one third of the days in pain, and very minimal number of missed days of activity, but underwent more dental procedures, took more medications for pain, and sought care with other providers, such as physicians and chiropractors (Nixdorf et al. 2016).

## 1.2 Rationale

This research focuses on assessing the predictive factors related to patient-reported severe post-operative pain, the frequency and source (*i.e.*, odontogenic and non-odontogenic) of persistent pain, and the impacts of severe post-operative pain and persistent pain on health-related quality of life. The pain-related factors associated with RCT are clinically important because severe post-operative pain is thought to be associated with impairment of function and degradation of quality of life of the patient experiencing it (Dugas et al. 2002, Law et al. 2014). As well, the pathway to chronic pain is thought to include severe post-operative pain (Katz and Seltzer 2009). The presence of persistent pain in association with RCT is important because it is difficult to treat (Lewis et al. 2007, Durham et al. 2013, Durham and Nixdorf 2014), is related to a greater amount of additional treatment (Durham and Nixdorf 2014, Nixdorf et al. 2016) and may impair quality of life (Durham and Nixdorf 2014, Shueb et al. 2015). These findings may also differ by whether the source of pain is odontogenic or non-odontogenic. This is important because further treatment directed towards the tooth

would be expected to exacerbate persistent pain (Durham et al. 2013, Durham and Nixdorf 2014).

### **1.3 Potential Risks and Benefits**

Research participants will not receive dental care as a study procedure; rather, patients will receive normal clinical care, including radiographs, as patients of participating practitioners. Risks of dental treatment provided as a part of normal care are not considered to be study associated.

#### **1.3.1 Potential Risks**

The primary potential risk to practitioners and patients is the possibility of breach of confidentiality. Appropriate precautions will be taken and procedures will be followed to maintain confidentiality. These include the use of unique study codes for participants, encryption of electronic data for transmission to the HealthPartners Institute Data Coordinating Center (HP IDCC), and password-protected computers for data storage. Compliance with all IRB regulations concerning data collection, data analysis, data storage, and data destruction will be strictly observed. Another risk of participating in this study for patients is the potential for psychological discomfort when answering some of the questions that are sensitive in nature. To reduce this risk, the patient will be allowed to skip any question that makes them feel uncomfortable. All questionnaires will be administered electronically with data sent directly to the study researchers, and the practitioner will not be allowed see patient responses.

#### **1.3.2 Potential Benefits**

Participation in the study will provide no direct benefit to patients. The potential benefits of this study are that the results may contribute to the evidence base about estimated risk for pain-related outcomes of RCT. In addition, this research may help guide the prioritization of further research in this area.

## 2 OBJECTIVES

### 2.1 Study Objectives

#### 3.1.1 Primary Objective

The primary objective is:

**Objective 1:** Develop a predictive model for severe post-operative pain experienced during the 7 days following completion of RCT, using pre- and intra-operative patient- and procedure- related factors.

#### 3.1.2 Secondary Objective

The secondary objective is:

**Objective 2:** Assess the proportion of patients reporting odontogenic and non-odontogenic persistent pain ( $\geq 1$  on scale of 0-10) at 6- and 12- months following RCT completion, and the impact of persistent pain on functional status and health-related quality of life at 12 months following RCT completion.

### 2.2 Study Outcome Measures

#### 3.2.1 Primary Outcome Measures

*Severe post-operative pain.* The primary outcome measure is severe post-operative pain, defined as the patient's self-reported worst pain intensity within the past 7 days that is  $\geq 7$  on a 0 to 10 numerical rating scale (adapted from the Graded Chronic Pain Scale), assessed one week following RCT completion.

*Predictors of severe pain.* To develop a predictive model for severe post-operative pain at one week following RCT completion, the following patient- and procedure-related factors will be assessed using data from the Patient Before- and After-Treatment Questionnaires, 1-Week (post-obturation) Questionnaires, Practitioner Before- and After-Treatment Questionnaires, and study team radiograph reviews:

- Pain characteristics (*i.e.*, intensity, duration, location)
- Psychosocial constructs (*i.e.*, catastrophizing, stress, anxiety, depression)
- Functional status and health-related quality of life (*i.e.*, JFLS, EQ5D5L)
- Medication use (*i.e.*, opioid exposure, antibiotic use)
- Patient socio-demographics (*i.e.*, age, gender, race, SES, BMI)
- Anatomical characteristics (*i.e.*, tooth type, canal curvature)
- Disease characteristics (*i.e.*, periapical radiolucency, vital pulp, swelling, tooth mobility)

- Procedural characteristics (*i.e.*, type of irrigant used, type of sealer used, single versus multiple appointments, use of rubber dam, over instrumentation/fill, one or more canals not negotiable within 2mm of the radiographic apex)
- Practitioner-reported before treatment case difficulty. Case difficulty is measured before and after treatment using a scale of 0 (easy) to 10 (very difficult), with the before treatment measure serving as the primary measure for the prediction model. The scoring strategy is used to evaluate the functional relationship (e.g., linear, quadratic, logarithmic, etc.) between scores and pain outcomes. After treatment case difficulty is collected by the practitioner and used for comparison with case difficulty assessment after RCT completion.
- Reasons for case difficulty are captured for any score  $\geq 3$  out of 10, and considered for model inclusion if the frequency or impact on post-operative pain is warranted. Blinded study staff with expertise in interpreting oral radiographs review before and after treatment radiographs to confirm practitioners' self-reported reasons for scoring case difficulty 3 or more on a scale of 0-10. Assessing the correspondence between practitioner and radiograph reviewer assessments is conducted to provide support for the use of case difficulty scores as a predictor of severe post-operative pain.

Measures of case difficulty have not been defined previously, even though the AAE publishes a Case Difficulty Assessment form that can be used to classify case difficulty in three levels: minimal, moderate, or high. The AAE Case Difficulty Assessment form is not practical for use in PREDICT, but does have components that can be assessed with relative ease. An ad-hoc AAE committee was formed, including Dr. Law and other AAE leadership, to develop a simplified set of questions and responses for use in PREDICT. These measures were further simplified to minimize practitioner burden while providing broad indicators of case difficulty that can provide a basis for future academic research for factors found to be influential components of practitioner-reported case difficulty. Thus, the importance of case difficulty as a predictor of post-operative pain appears relevant, though ill-defined. Given this limitation, we believe the measurement strategy used in PREDICT is an efficient method of capturing basic information on factors that the AAE Ad-hoc committee believe are relevant.

### 3.2.2 Secondary Outcome Measures

1) *Persistent pain at 6 and 12 months.* Persistent pain is defined as patient-reported pain lasting 1 or more days in the last 30 days and, at an average pain intensity of  $\geq 1$  on a 0-10 Graded Chronic Pain Scale. Persistent pain will be assessed at 6 and 12 months following RCT completion (*i.e.*, obturation). Six months is the time point that defines persistent pain according to the pain literature.

2) *Odontogenic and non-odontogenic persistent pain.* Persistent pain at 12 months will be further categorized as: a) odontogenic (e.g., symptomatic apical periodontitis, excessive occlusion forces, adjacent tooth), and/or b) non-odontogenic (e.g., TMD, trigeminal neuralgia, deafferentation pain, sinusitis) by practitioner assessment after clinical examination and practitioner radiographic interpretation, if applicable. Practitioners will make these determinations using their regular process performed in clinical practice.

3) *Radiographic confirmation.* If available, pre/post-operative and 12-month periapical radiographs will be assessed for evidence of healing, defined as:

1. Presence of periapical/periradicular lesion of endodontic origin at baseline and, using available follow-up radiographs, indication of radiographic evidence of inflammation (yes/no/unsure)
2. Appearance indicating that healing has occurred (yes/no/unsure) and absence of an indication of radiographic evidence of inflammation (yes/no/unsure) at 12-months

Study staff with expertise in interpreting oral radiographs will independently evaluate radiographs for evidence of healing and an absence of inflammation at 12-months. The radiographic assessment will define case status of odontogenic versus non-odontogenic origin of persistent pain and will be used to establish concordance with the practitioner's pain assessment.

4) *Temporomandibular Disorders pain (TMD) and Persistent Dentoalveolar Pain disorder (PDAP).* Two patient self-reported instruments will screen for two common non-odontogenic causes of orofacial pain among patients with persistent pain: The 6-item Temporomandibular Disorders (TMD) Screener (Gonzalez et al. 2011) and the 14-item Persistent Dentoalveolar Pain disorders (PDAP) Screener (publication pending). The patient screener responses, radiographic assessments, and practitioner pain assessments will be used to ascertain the case status (*i.e.*, odontogenic/non-odontogenic). Odontogenic/nonodontogenic pain determination and persistent pain etiology (*i.e.*, TMD, PDAP) will be calculated for patients with persistent pain providing 6- and 12- month data.

5) *Functional status and health-related quality of life (QoL) assessment.* Patient-reported jaw function will be assessed using the 8-item Jaw Function and Limitation Scale (JFLS) (Ohrbach et al. 2008a, Ohrbach et al. 2008b). Overall function will be measured using the 5-item EuroQol (EQ5D5L), a measure of general QoL instrument, which has been demonstrated to respond to differences in patients with persistent orofacial pain (Durham et al. 2015). The use of both functional status measures allows for assessment of body-region specific function and general function, as well as comparison of other disorders affecting the body-region and general health. Patient responses to each of the 5 dimensions of health are combined into an index score

measuring overall quality of life between 0 (dead) to 1.0 (perfect health). This score enables comparisons across health conditions. Measures will be obtained at 1-week and 12-months following RCT.

6) *Factors that may contribute to pain impact.* The practitioner will record tooth status, additional treatment on the tooth, and characteristics of the restoration 12-months following RCT. Patients medication use and psychosocial variables (e.g. catastrophizing) will be ascertained at 6- and 12- months following RCT. See Section 7 for additional detail.

7) Case difficulty measurement. Practitioner-reported case difficulty is measured before and after treatment using a scale of 0 (minimal), 5 moderate, to 10 (high) following the AAE Case Difficulty Assessment Form definitions, with the before treatment measure serving as the primary measure for the prediction model. The anchors for the range are minimal, moderate, and high case difficulty. Practitioners will be trained to define minimal as a "condition indicating routine complexity (uncomplicated)", following the AAE Case Difficulty Assessment Form (available at AAE.org). Moderate case difficulty will be considered a "condition that is complicated, exhibiting at least one patient or treatment factors below that the practitioner rates as moderately difficult". Practitioners will be asked to specify which factor is the source for the rating if the overall rating is 3 or more. High case difficulty is defined as a "condition that is exceptionally complicated, exhibiting at least one factor that is exceptionally complicated or five or more moderately difficult factors. The purpose of this measure is not to differentiate the case difficulty level for any single factor, which is beyond the scope of this study, but to understand the factors that influence practitioners' overall case difficulty ratings.



### 3 STUDY DESIGN

This is a 12 month prospective observational study of patients receiving initial orthograde RCT by general dentists and endodontists participating in the National Dental PBRN. Participating practitioners will be asked to use a consecutive patient recruitment strategy, adapted to fit practice constraints among individual dentists (see Section 5), to control for selection bias. All data will be obtained electronically at the following time points: in-office at RCT initiation during the baseline visit and after RCT treatment completion (obturation) for patients requiring multiple visits, 1 week and 6 months following RCT completion online or via telephone (no in-office visit), and 12 months following RCT completion via in-office visit or online/telephone if data cannot be obtained with an in-office visit. All patients will complete the Before and After Treatment Questionnaires at the baseline visit. The coordinating center or regional staff will follow-up with patients that do not complete one or both of the questionnaires at baseline. About 80% of patients are expected to require multiple visits to complete their RCT. For these patients, the practitioner will complete the Before Treatment Questionnaire at the baseline visit, and complete the After Treatment Questionnaire (and radiograph upload) at the RCT completion visit.

**Practitioner recruitment:** The study team and regional staff will recruit approximately 175 network dentists who perform RCT routinely (approximately 1 per week) from six regions. A target mix of approximately 115 general dentists and 60 endodontists will be recruited to enable a wide range of patient characteristics, case difficulty, and treatment methods to be captured. A reasonable distribution of recruited practitioners by region will be sought.

**Study population:** During a target 4-6 month patient enrollment period, approximately 2,000 adult patients undergoing RCT will be consented for study participation (see Schematic of Study Design). See inclusion and exclusion criteria in Section 4 below. Previous research indicated that about 10% of patients failed to complete the RCT treatment. Assuming a similar loss-to-follow up rate, we expect approximately 1,500 enrolled patients to complete RCT treatment.

**Data collection:** Consent will be administered electronically or on paper, and data will be collected via electronic means for the entire study. Patient-reported data will be collected via tablets, smart-phones, or computers during in-office visits and other time points. To assist with in-office data collection, practitioner participants will be offered tablets. Office personnel will not have access to any patient-reported data. Practitioners will provide clinical examination and procedural data electronically via tablets, smart-phones, or computers. HealthPartners Institute Data Coordinating Center (HP IDCC) will manage follow-up contacts of non-responders.

Patients who do not present to the dental office at 12 months will be contacted by the HP IDCC requesting completion of the Patient 12-Month Questionnaire, either electronically or via telephone with the HP IDCC personnel.

**Radiographs:** Periapical radiographs will be captured at three time-points as part of standard care: 1) before RCT treatment; 2) after RCT completion; and 3) at the 12-month follow-up visit. These images will be digitally uploaded to the study's website by the practitioners or study trained staff. A blinded and trained endodontist and oral radiologist will independently review pre/post-operative and 12-month radiographs using consistent evaluation criteria. A third evaluator will be used if the two blinded evaluators differ in opinion. See Section 7 for more detail.

## 4 STUDY ENROLLMENT AND WITHDRAWAL

### 4.1 Inclusion Criteria

**Practitioners:** To be eligible to participate in this study and recruit patient participants, a practitioner must be deemed study ready by their Regional Administrative Site (RAS) and meet the following criteria:

- Be willing to provide consent according to regionally approved procedures;
- Be a dentist or endodontist who performs approximately one (1) RCT per week ;
- Be available to perform 12 month follow-up examinations for enrolled patients;
- Have the ability to receive emails and access online questionnaires; and
- Be able to provide radiographs in electronic format (i.e., jpeg, Digital Imaging and Communications in Medicine [DICOM] or tif).

**Patients:** To be eligible to participate in this study, a patient must meet all of the following eligibility criteria:

- Age  $\geq$  18 years, except in Nebraska where consent is age  $\geq$  19 years;
- Be willing to provide consent according to regionally approved procedures;
- Have *one* permanent tooth undergoing initial orthograde root canal treatment;
- Anticipate being available for a clinical follow-up at 12 months;
- Be able to provide contact information for one other person with a different phone number who will know the patient's whereabouts in the event the patient cannot be reached;
- Have the ability to receive emails and access online questionnaires;
- Be willing to be contacted by each of these entities: the practice, regional coordinators, and the HP IDCC.

### 4.2 Exclusion Criteria

**Patients:** An individual who meets any of the following criteria will be excluded from participation in this study:

- Evidence of treatment having been initiated for an iatrogenic pulpal exposure (cases with a carious exposure of the pulp will not be excluded);

- More than one tooth requiring root canal treatment at the time of enrollment (occurs rarely and not expected to inhibit recruitment);
- Previously enrolled in the study;
- Obvious cognitive impairments that preclude participation in the informed consent process or ability to complete study activities (e.g., previous stroke with communication deficits, dementia)
- Inability to understand study procedures or provide consent in English or Spanish.

### **4.3 Strategies for Recruitment and Retention**

#### **4.3.1 Practitioner Recruitment:**

Practitioner recruitment will be led by the study team in collaboration with regional staff and interested professional organizations. Practitioner recruitment emails will be developed and tailored by each region. The network practitioner database will be used to identify general dentists and endodontists for email recruitment and follow-up. Additional strategies will include, but are not limited to, identifying dentists and the media that they consume via the American Association of Endodontists (AAE), and State and Regional Dental Associations, and developing and executing the messaging in print, electronic and web-based media. Further, members of the Endodontic Interest Group, a group of dentists and endodontists recruited at the Midwest Regional Meeting in 2013, will be asked to invite their colleagues and staff to the booth during the AAE Annual Session. These practitioners hold positions in national and regional dental organizations and have expressed willingness to advocate for study participation.

Practitioners will receive \$50 remuneration for each enrolled patient who completes the Patient Before-Treatment and Patient After-Treatment Questionnaires, and for whom the dentist completes the Practitioner Before-Treatment and Practitioner After-Treatment Questionnaires, and uploads pre- and post-RCT completion radiographs. Practitioners will receive \$50 even if the patient does not attend the RCT completion visit as long as the practitioner submits the before treatment assessments and radiographs. Practitioners will be remunerated \$35 for the 12 month in-office patient evaluation and radiograph submission. Each practitioner will also be allowed to keep a study-purchased tablet computer (approximately \$200 each) that will be used for data collection in the clinic. Practitioner remuneration will be up to \$85 per patient with the value of the tablet (\$200) included as part of the total remuneration.

#### 4.3.2 Patient Recruitment:

Approximately 2,000 patients requiring a single root canal treatment will be recruited over a total study recruitment period of 4-6 months. Following protocol training, each practitioner will be asked to enroll a *target* of 7 (general dentists) and 15 (endodontists) patients. Targeted enrollment numbers and periods (see below) may vary in order to cost-effectively meet overall study recruitment targets. Further, enrollment targets differ between general dentists and endodontists to reflect differences in the number of RCTs performed in a typical week.

Practitioners will be asked to use a consecutive enrollment strategy for a target 10-14 week patient enrollment period, or until the end of the study enrollment period. Each practitioner will establish a regular recruitment period (days and/or times) each week that fits the practice and is sufficient to meet enrollment targets. A screening criteria log will be used to record potential patient refusal/non-enrollment and, where allowed, reasons for non-enrollment, during established recruiting periods. Practitioner's recruitment schedules may be adjusted at any time with the consultation of the Regional Coordinator (RC).

General dentists (n=115) will enroll a target of approximately 800 patients (about 7 each), with an approximate maximum of 50 per dentist to allow for substitution for under-enrolling dentists. This provides a target of approximately 720 patients with an RCT completion visit, assuming a 10% non-completion rate.

Endodontists (n=60) will enroll a target of approximately 867 patients (15 each), with an approximate maximum of 50 per endodontist to allow for substitution for under-enrolling practitioners. This provides a target of approximately 780 patients with an RCT completion visit, assuming a 10% non-completion rate.

The overall study recruitment period, and practitioner-specific recruitment numbers and time periods, will provide sufficient flexibility for the study to meet its enrollment target. The study statistician indicated that clusters of up-to approximately 50 patients will not adversely affect study outcome analyses. We expect general dentists will need more time to meet recruitment targets compared to endodontists. Thus, to the extent possible, RCs in each region will prioritize training for general dentists to provide general dentists with more time to complete recruitment.

### **4.3.3 Patient Retention:**

Patient retention is important to this study and most follow-up data will be collected independent of a clinic visit. The Patient Retention Plan is presented in Appendix B. Study patients will be asked to complete follow-up questionnaires online at 1 week following completion of RCT, 6 months and 12 months (if they do not report to the office for a 12 month evaluation). Patients will be remunerated for completed questionnaires at each time point: \$20 at RCT completion, \$20 at 1 week, \$25 at 6 months, \$50 for completing the 12 month questionnaire, and an additional \$50 for completing the clinical evaluation at 12 months. Patients completing all assessments will receive a total remuneration of \$165.

Study patients will be contacted by email prior to each follow-up data collection interval. The initial email communication for each survey period will include the request to complete the questionnaire and an active link to the online web-based questionnaire. The HP IDCC staff will use email, telephone and/or text messages to follow-up with non-responders prior to the close of data collection window to encourage them to complete questionnaires. When contacted, patients will be given the option to complete the questionnaires by telephone with the HP IDCC.

### **4.3.4 Practitioner Retention:**

Practitioner retention is important to this study. The study leadership and regional coordinators will maintain efforts to engage practitioners throughout the duration of the study, including addressing practitioner questions and concerns and informing them about study results after data analysis has been completed.

## **4.4 Practitioner and Patient Withdrawal**

### **4.4.1 Reasons for Withdrawal**

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

A practitioner may terminate a patient's participation in the study if:

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

includes patients that complete the study who may be excluded from the data analysis.

#### **4.4.2 Handling of Patient Withdrawals**

In the case of patient withdrawal from the study, the study will only attempt continued follow-up data collection for patients who are withdrawn due to an unanticipated problem (UP) or other safety concerns. In those cases, only data related to the completion of reporting requirements for the UP will be recorded. Patients withdrawn from the study for any other reason will have the date and reason for withdrawal recorded, but no additional study data will be collected. Patients withdrawn from the study may continue to receive normal clinical care as patients of the participating dentists.

#### **4.5 Premature Termination or Suspension of Study**

This study may be suspended or prematurely terminated if there is sufficient reasonable cause, which will be a decision of the investigators or NICDR. 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 Grant Principal Investigator will promptly inform the IRB and will provide the reason(s) for suspension or termination.

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

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

## **5 STUDY SCHEDULE**

Practitioners enrolled in the National Dental PBRN who express interest in the study and meet eligibility criteria will be invited to participate. Study information and instructions will be provided to interested practitioners by the regional staff including the patient selection procedures, methods for approaching patients and obtaining informed consent (according to regional approvals), methods for data collection, and other study procedures. In addition, RCs will conduct in-person or remote protocol training with practitioners and staff prior to initiating the study. The training ensures that the practitioner and staff understand the study procedures and receive instruction on the consent process, the electronic data capture system, and the radiographic upload. The RCs will maintain close contact with the practitioners prior to and throughout the study implementation period.

The study schedule will proceed in the following stages on a rolling basis:

- 1) Each region will enroll practitioners into the study to obtain a total of approximately 175 across all regions. A reasonable balance across regions is preferred but not required;
- 2) Practitioners will complete activities to be deemed study-ready;
- 3) RCs will train study-ready practitioners and their office staff in the appropriate study procedures; and
- 4) Practices will screen and enroll eligible patients into the study.

The HP IDCC, along with the Regional Administrative Site (RAS) and RCs, will coordinate the launch of the study. For each of the six regions, participating practitioners will be enrolled over a period of approximately 4-6 months. Practitioners will begin study recruitment as soon as possible following study training with an RC.

### **5.1 Practitioner Enrollment/Baseline**

- Verify practitioner inclusion/exclusion criteria;
- Obtain and document consent according to regional IRB requirements; and
- Practitioner and eligible staff participate in study training with an RC.

### **5.2 Patient Screening/Enrollment**

Prospective patients may be recruited at any dental appointment in a participating practitioner's office when it is determined that a patient will need a RCT. The practitioner or staff member will introduce the study to the patient and review inclusion and exclusion criteria via a study-issued tablet. If eligible and interested in the study, the patient will undergo the consenting process via the tablet, pursuant to overseeing IRB requirements. If an eligible patient wishes to decline participation in the study, this occurrence will be noted in the screening log, and the informed consent process will not be completed.



Together, patient and practitioner will:

- Verify patient inclusion/exclusion criteria
- Obtain and document consent according to regional IRB requirements
- Obtain and document HIPAA according to regional IRB requirements

### **5.3 Patient Baseline (Study Visit (SV) 1 = Day 0)**

If the RCT is completed in one appointment, the **patient** will:

- Complete the Patient Contact Form
- Complete the Patient Before-Treatment Questionnaire (prior to and after administration of local anesthesia)
- Complete the Patient After-Treatment Questionnaire (following treatment initiation and before leaving the dental office)

During or after the appointment, the **practitioner** will:

- Complete the Practitioner Before-Treatment Questionnaire
- Complete the Practitioner After-Treatment Questionnaire
- Complete the practitioner dentist section of the modified AAE Endodontic Case Difficulty Form
- Upload diagnostic and obturation periapical radiographs, if obtained for clinical care purposes

**If the RCT is not completed at this appointment the patient will:**

- Complete the Patient Contact Form
- Complete the Patient Before-Treatment Questionnaire (prior to and after administration of local anesthesia)
- Complete the Patient After-Treatment Questionnaire (following treatment initiation and before leaving the dental office)

During or after (but on the same day as) the appointment, the **practitioner** will:

- Complete the Practitioner Before-Treatment Questionnaire

#### **5.4 Completion of RCT-Multiple Appointments**

Enrolled patients may have an additional visit between the enrollment and RCT completion visits. No data are collected at these visits.

##### **At the RCT completion visit**

During or after the appointment, the **practitioner** will:

- Complete the Practitioner After-Treatment Questionnaire
- Upload diagnostic and obturation periapical radiographs, if obtained for clinical care purposes

#### **5.5 1 Week Post Completion of RCT (SV2: Completion date +7 days, range 7-14 after completion)**

- The patient completes the Patient 1-Week Questionnaire electronically or via telephone

#### **5.6 6 Months Post Completion of RCT (SV3: Completion date +180 days, target range 180-210 after completion)**

- The patient completes the Patient 6-Month Questionnaire electronically or via telephone

#### **5.7 12 Months Post Completion of RCT (SV4: Completion date +365 days, target range 305-455 after completion)**

If the patient reports to the office:

The **patient** will:

- Complete the Patient 12-Month Questionnaire in-office

The **practitioner** will:

- Complete an examination on the RCT treated tooth
- Complete the Practitioner 12-Month Questionnaire
- Upload periapical radiograph(s) obtained for clinical care purposes

If the patient does not report to the office:

- The **patient** will complete the Patient 12-Month Questionnaire electronically or via telephone

## **5.8 Withdrawal**

When a patient withdraws from the study, the following is completed:

- Withdrawal date and reason for withdrawal is documented
- Consistent with Section 4.4.2, the only evaluations and data collection authorized will be information needed to address an UP or other safety issue that may have led to his/her withdrawal from the study

## 6 STUDY PROCEDURES/EVALUATIONS

The intent of this observational study is to observe usual clinical care provided by the participating dentists and not to influence or manipulate diagnostic or treatment procedures. We selected our predictive variables based on published research from the dental literature, which generally have focused on anatomic, disease, and procedure variables (Keiser and Byrne 2006, Law et al. 2015, Nixdorf et al. 2016), and from the pain literature, which generally have focused on pain characteristics, psychosocial, functional and quality of life variables (Althaus et al. 2012, Pinto et al. 2012, Pinto et al. 2013, Althaus et al. 2014, Burns et al. 2015, Lewis et al. 2015).

### 6.1 Study Procedures/Evaluations and Questionnaire Administration

All baseline and follow-up data will be collected electronically.

#### Practitioners

Baseline: Practitioners will complete the *Practitioner Before-Treatment Questionnaire* and *Practitioner After-Treatment Questionnaire*, which includes portions of the modified AAE Endodontic Case Difficulty Assessment Form. The questionnaires will be completed based upon examination and treatment performed to record: 1) what tooth is being treated; 2) signs and symptoms to derive endodontic diagnoses; 3) case difficulty assessment; 4) other tooth characteristics; 5) analgesia/anxiolysis provided; 6) procedural details of care performed; and 7) post-treatment prescriptions provided.

Case difficulty will be assessed with the AAE Endodontic Case Difficulty Assessment form, modified by a committee of experts (*i.e.*, AAE's *ad hoc* PBRN committee), for use in regular clinical practice, with the items vetted by practitioners within the network.

Twelve Months: Practitioners will complete the *Practitioner 12-Month Questionnaire* based upon clinical examination and radiographic interpretation (if applicable), to record information related to: 1) tooth status and additional treatment; 2) characteristics of restoration; 3) signs and symptoms related to initial endodontic diagnoses; and 4) odontogenic/non-odontogenic pain assessment if present.

Radiographs: Practitioners will submit periapical radiographs taken before treatment, after treatment (*i.e.*, following obturation), and at 12 months, if obtained for treatment purposes. Twelve months is the earliest time when changes within the periapical bone can reliably be detected with PA radiographs (Orstavik 1996).

#### Patients

Patient questionnaires will ascertain pain and psychosocial factors thought to be important predictors for post-operative pain. In addition, jaw function will be measured with the JFLS and general health quality of life with the EQ5D5L to assess the impact of

pain upon these factors (see Section 3.2). The JLFS and EQ5D5L are within the Patient one week and 12- Month Questionnaires. Finally, self-reported TMD will be measured with the TMD screener and persistent dentoalveolar pain with the PDAP screener. Both Screeners are scored using a numeric scale, 0 to 7 for the 6-item TMD Screener (Gonzalez et al. 2011) and -28 to 28 for the 14-item PDAP Screener (publication pending). A threshold score of  $\geq 3$  denotes a positive screen for both the TMD Screener (Gonzalez et al. 2011) and the PDAP Screener (publication pending). The TMD Screener and the PDAP Screener questions are within the Patient 6- and 12- Month Questionnaires. The patient screener responses, practitioner pain assessments, and radiographic assessments will be utilized to ascertain the case status as odontogenic and/or non-odontogenic pain.

Baseline: Patients will complete the Patient Before-Treatment Questionnaire and Patient After-Treatment Questionnaire, which will ascertain information related to: 1) demographics; 2) socioeconomic variables; 3) tooth pain characteristics; 4) TMD pain; 5) medication use; 6) exposure to opioid-based substances; 7) treatment expectation; 8) dental fear; 9) anxiety; 10) depression; 11) perceived stress; and 12) catastrophization; . Patient demographics, SES, and intra-operative pain are assessed after baseline visit treatment and before leaving the dental office, all other pain and psychosocial-related measures are assessed before treatment is initiated.

One Week: Patients will complete the Patient 1-Week Questionnaire following completion of RCT to ascertain information related to: 1) tooth pain characteristics; 2) pain-related interference in daily life; 3) medication use; 4) jaw function; 5) general health quality of life; 6) demographic and socioeconomic variables; 7) diabetes status; 8) measure of widespread pain; 9) self-reported body mass index; and 10) smoking status.

Six Months: Patients will complete the Patient 6-Month Questionnaire to ascertain information related to: 1) tooth pain characteristics; 2) TMD and persistent dentoalveolar pain; 3) medication use; 4) exposure to opioid-based substances; 5) catastrophization; and 6) jaw function.

Twelve Months: Patients will complete the Patient 12-Month Questionnaire to ascertain information related to: 1) tooth pain characteristics; 2) TMD and persistent dentoalveolar pain; 3) medication use; 4) exposure to opioid-based substances; 5) jaw function; and 6) general health quality of life.

Origin of selected items:

- Tooth pain characteristics, pain-related interference in daily life: adopted without modification from the Graded Chronic Pain Scale (GCPS) (Von Korff et al. 1992)

- Anxiety: Two-item General Anxiety Disorder (GAD-2) questionnaire, derived from GAD-7 questionnaire (Spitzer et al. 2006, Schalet et al. 2014), has been used in pain populations (Seo and Park 2015a)
- Depression: Two-item Patient Health Questionnaire (PHQ-2) (Kroenke et al. 2003), has been used in pain populations (Menendez et al. 2015, Seo and Park 2015b)
- Perceived stress: Four-items derived from the Perceived Stress Scale (PSS) (Cohen et al. 1983), validated (Ingram et al. 2016), and shown to have predictive value (Carroll et al. 2015)
- Catastrophization: Two items have been validated (Jensen et al. 2003) and found to have predictive value by others (Benyon et al. 2013)
- Treatment expectation: developed during the previous PBRN Study 17/18
- Dental fear: One-item instrument derived from the survey work performed by the Dental Fears Research Clinic (Milgrom et al. 1988)
- Global health status: adopted without modification from Nurses' Health Study 2
- Diabetes status, body mass index: adopted without modification from Behavioral Risk Factor Surveillance System (BRFSS) survey
- Fibromyalgia status: a single item associated with the presence of chronic widespread pain, used in place of a multi-item FMS screener from Hauser et al., 2012.
- General health quality of life: Five-item, five-level questionnaire developed by EuroQual Group <http://www.euroqol.org> and validated in many populations, including orofacial pain patients (Durham et al. 2015)

## 6.2 Development of data collection instruments

Questionnaire development has included refinement of data collection instruments with an emphasis on reducing overall burden and improving acceptability. Questionnaires have been developed from validated instruments, when possible, that have been modified and/or combined with other instruments. When choosing validated instruments, short screeners that have limited items were prioritized if they addressed the domains of interest to limit burden of implementation.

Practitioner and patient questionnaires to be utilized in this study have undergone an iterative process of pilot testing and refinement. Study team Practitioners and the Endodontic Interest Group have asked their patients to complete the questionnaires and requested feedback on their understanding of the content in general, sensitivity/appropriateness of content for the setting, and length of time necessary for completion. This testing has taken place in dental offices. Similarly, the practitioner questionnaires have been tested in a regular practice setting by members of the Endodontic Interest Group and the AAE's ad hoc PBRN committee. Feedback was

received on their ability to understand what is being asked, applicability of the topics included, and length of time necessary for completion.

### **6.3 Radiographic Assessment**

An oral & maxillofacial radiologist and an endodontist will independently interpret each radiograph, respond to a set of questions related to the image on the Radiograph Interpretation Form and develop a consensus opinion about whether a lesion of endodontic origin was present (see outcome measures in Section 3.2). If the radiologist and endodontist are unable to reach consensus, the Study PI (Dr. Nixdorf) will be notified and will be responsible for making a final determination. The evaluations will be used to provide independent confirmation of the evidence of healing assessment provided by practitioners. The presence of a lesion on the before treatment radiograph established the baseline odontogenic etiology of the tooth condition and patient-reported pain. At 12-month follow-up, two questions are used to differentiate the odontogenic or non-odontogenic radiographic source of pain. The radiographic indication of inflammation and the absence of evidence indicating healing will be used to define patient-reported pain at 12-months as being odontogenic in etiology. This radiographic analysis process will also be supported by the study's electronic application.

## 7 ASSESSMENT OF SAFETY

### 7.1 Specification of Safety Parameters

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

#### 7.1.1 Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to patients 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 patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

#### 7.1.2 Serious Adverse Events (SAE)

A serious adverse event 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.

### 7.2 Reporting Procedures

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an UP report form. OHRP recommends that investigators



include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

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

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

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

All UP 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

## **8 STUDY OVERSIGHT**

Study oversight is provided by the Grant PI, Study PIs, and relevant regional institutional review boards. This study uses a multiple-PI model. Study principal investigators (SPIs) are Dr. Nixdorf, associate professor and orofacial pain practitioner at the University of Minnesota, and Dr. Fellows, health economist and investigator at the Kaiser Permanente Center for Health Research (CHR) and Western Region Director. Dr. Fellows is the Contact SPI for this study.

The multi-PI arrangement for this study brings together the complementary expertise and experience of the two SPIs. Dr. Nixdorf has expertise in orofacial pain, pain-related treatment and outcomes evaluation, and clinical practice. Dr. Fellows has expertise and experience conducting multi-site clinical trials as part of routine clinical care, practice-based research methodology, and health outcomes evaluation. Drs. Nixdorf and Fellows will work collaboratively to ensure the success of the study, and will meet weekly to review study progress, address challenges, and identify action plans and deliverables.

Dr. Nixdorf will have primary responsibility over scientific issues related to dental care, pain measurement, and pain-related outcomes evaluation. Working collaboratively with study coordinating center staff, Dr. Fellows will have primary responsibility over study management, including study implementation and quality control, study team communications, budget monitoring, and reporting. Disagreements will be resolved through discussions with the study team and coordinating center PI, and if necessary the Grant PI and NIDCR Project Officers. Dr. Fellows will have primary decision-making authority for conflict resolution.

In addition, study oversight will be provided under the direction of the NIDCR Medical Monitor. The SPIs will submit reports to NIDCR Medical Monitor for review at six month intervals after study initiation until enrollment targets have been met, and then annually thereafter. Medical Monitor reports will include data regarding enrollment and retention, unanticipated problems and protocol deviations, primary outcome measures, quality management findings and other relevant parameters. If necessary, additional steps may be taken to ensure data integrity and protocol compliance.

## 9 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.

Remote monitoring activities will primarily involve quality management (QM) to ensure completeness and accuracy of data collection. These QM procedures are described in the protocol, Sections 12 and 14, as well as the study specific Manual of Procedures (MOP). This study will follow the general guidelines for conducting in-office monitoring for the network's observational clinical studies documented in Chapter 6 of the National Dental PBRN Manual of General Operations. Documentation of monitoring activities and findings will be provided to the practitioner, GPI, and SPIs, OCTOM and [NIDCR.NIDCR\\_Reports@rhoworld.com](mailto:NIDCR.NIDCR_Reports@rhoworld.com). The NIDCR reserves the right to conduct independent audits as necessary.

## 10 STATISTICAL CONSIDERATIONS

### 10.1 Study Hypotheses

This is a descriptive study and is therefore hypothesis-generating in nature.

### 10.2 Sample Size Considerations

The main consideration in choosing a sample size was to ensure that the study has enough events to support analysis of the binary (yes/no) dependent variable severe post-operative pain 1-week after RCT completion, using logistic regression with at least 15 predictors. The goal was to provide ample power for finding associations between individual predictors and such a binary outcome.

The frequency of severe post-operative pain was estimated to be 19.5% (95% CI: 16.5% to 22.7%) in previous network research (Law et al. 2015). In that study, the required 1-week data was collected in 92.1% of patients (Nixdorf et al. 2012); missing data used in the regression analysis ranged from 9.2% when 7 variables were in the model to 11.8% when 13 variables were used (Law et al. 2015). We therefore assume that in the present study, 20% of participants will not provide data for the primary analysis, with 10% lost to follow up and 10% having missing values for predictors.

Using the rule of thumb that 15 events are needed for each predictor included in the model, enrolling 2,000 participants will provide enough events for 1,500 patients who complete 1-week post RCT to allow 16 predictors to be included in the final regression model (see Table below). Alternate rules of thumb requiring 10 or 20 events per predictor imply that our sample size can support 12 to 24 predictors.

Table. For possible sample sizes, numbers of predictors supported

Sample Size	1000	1250	<b>1500</b>	1750	2000
Number of cases (@ 20%)	200	250	<b>300</b>	350	400
Cases after 20% loss	160	200	<b>240</b>	280	320
Non-cases after 20% loss	640	800	<b>960</b>	1120	1280
Total participants after 20% loss	800	1000	<b>1200</b>	1400	1600
Number of predictors: @10 events/pred	16	20	<b>24</b>	28	32
@15 events/pred	11	13	<b>16</b>	19	21
@20 events/pred	8	10	<b>12</b>	14	16

This sample size provides sufficient power to assess the association of individual binary or continuous predictors with the primary outcome, a binary (1/0) measure of severe post-operative pain. It also provides sufficient power to assess the association of

individual binary or continuous predictors with continuous outcomes (*i.e.*, some of the secondary outcomes).

For a binary predictor, power depends on the sizes of the two groups created by that binary predictor, with power being greatest if the two groups have equal sizes and dropping as the sizes of the groups become more different. We have selected and defined binary predictors so that neither of the groups defined by a predictor's two categories is small. Below, we present a conservative power computation for a binary predictor that creates two groups with sample sizes having the ratio 3:1.

The primary outcome is a binary (1/0) measure of severe post-operative pain with an expected marginal rate of 20%. The study design and sample size provide 80% power to detect impact rates on outcome for binary predictors with differences between those two groups if the outcome rates are 26% in the smaller group and 18% in the larger group (relative risk 1.44, odds ratio 1.6).

The study design and sample size provide substantial power to detect associations between the binary dependent variable and predictors measured on a continuous scale. The primary outcome has marginal rate 20%, as assumed above; our design provides 80% power to detect an odds ratio for this outcome of less than 1.3 for a one-standard deviation change in the continuous predictor.

Our design and sample size provide even more power for continuous outcomes (*i.e.*, some of the secondary outcomes). For a binary predictor of this continuous outcome, we have 80% power to detect a difference with Cohen's *d* of 0.2 between the two groups created by the binary predictor. For a continuous predictor of the continuous outcome, our design provides 80% power to detect an association in which a one standard deviation change in the predictor is associated with a change of 8.1% of the standard deviation of the outcome variable, *i.e.*, the standard deviation before removing the effect of any predictors.

### **10.3 Final Analysis Plan**

#### Analyses for Primary Objective

The primary objective is to develop a predictive model for severe post-operative pain experienced during the 1-week following RCT completion, using pre- and intra-operative patient-, disease- and procedure-related factors. Severe pain is defined as patient-reported pain intensity rating of  $\geq 7$  on a 0-10 numeric rating scale.

The predictive model will be developed using a step-wise regression approach with patient, disease and procedural factors obtained before and after RCT treatment completion. First, univariate analyses will assess the relationship between individual

factors and severe post-operative pain, obtained from the patients' and dentists' Before and After Treatment Questionnaires. Second, individual factors with significance of  $p \leq 0.15$  will be included in a multiple-variable stepwise regression model. Main effects and all 2-level interactions between predictors and outcomes will be assessed. Main effects and interactions with significance level of  $p \leq 0.10$  will be retained for the final model. Third, we will rerun the outcome analysis with the final model specification and report parameter estimates, standard deviations, adjusted odds ratios and 95% confidence intervals, and predicted probabilities of severe pain, overall and by predictor. Final decisions about which predictors and interactions to retain are expected to be made using the Schwarz criterion (also known as the Bayesian Information Criterion [BIC]), which has better large-sample properties and tends to prefer smaller models compared to Akaike's Information Criterion [AIC].

Predictors to be considered will include these domains measured at baseline and intra-operatively: pain (*i.e.*, intensity, duration, wide-spread), psychosocial (*i.e.*, catastrophizing, stress, anxiety, depression), medication use (*i.e.*, opioid exposure), personal characteristics (*i.e.*, demographics, SES, BMI), anatomical characteristics (*i.e.*, maxillary molar, canal curvature), planned procedural characteristics (*i.e.*, type of irrigant used), and aspects of the procedure performed (*i.e.*, over instrumentation/fill, one or more canals not negotiable within 2 mm of the radiographic apex).

Treatment is expected to involve multiple visits for about 20% of the enrolled patients. Only two study visits are considered: the enrollment visit when RCT treatment begins and the RCT completion visit. Any additional visits between these two time points are not assessed. The actual number of visits (1 vs.  $\geq 2$ ) will be included in the prediction model. In addition, the number of days between treatment initiation and completion will be captured and considered for analysis. The date of the RCT completion is the reference date for the 1-week follow-up assessment.

We will assess the model using out-of-sample predictive checks. We will set aside a randomly-chosen training set consisting of 80% of the participants, fit the chosen model to it, predict the remaining 20% (the test set), and compare predicted vs. actual fractions in subgroupings of interest (using, *e.g.*, Hosmer-Lemeshow tests). This procedure will also be used to test for biases in subgroup of interest.

### Analyses for Secondary Objectives

1) Proportion of patients reporting persistent pain, defined as a dichotomized numerical pain rating of  $\geq 1$  on a 0-10 average pain intensity scale and  $\geq 1$  day of pain over the last month (*i.e.*, 30 days). This will be calculated for patients at 6 months and 12 months following root canal treatment, with 95% confidence intervals (CI). The mean, median, and range of pain severity will be reported, overall and by group based on pre- and post-operative pain severity. The proportion of patients with no persistent pain, with 95% confidence intervals, will also be reported.

2) Patients with odontogenic and non-odontogenic persistent pain are defined as first meeting the criteria for persistent pain (see above) and are further categorized as: a) odontogenic (e.g., symptomatic apical periodontitis, excessive occlusion forces, adjacent tooth), and/or b) non-odontogenic (e.g., TMD, trigeminal neuralgia, deafferentation pain, sinusitis) by practitioner assessment after clinical examination and practitioner radiographic interpretation, if applicable. Proportions, with 95% CIs, will be calculated, and mean, median, and range of pain severity will be reported, overall and by group based on pre- and post-operative pain severity.

3) Existing radiographic evidence will be used to confirm non-odontogenic pain case status (odontogenic/non-odontogenic), which was assessed with the practitioner's rating (see above). To confirm non-odontogenic pain status, independent study examiners must find evidence of healing on the radiograph (defined in Section 7.3). Conversely, concordance between absence of radiographic evidence of healing and odontogenic pain assessment will be used to confirm odontogenic case status. Discordant cases will not be given a confirmatory status. All groups will be described in a similar fashion as listed above (i.e., proportions, 95% CIs, mean, median, range by groups).

4) Among patients determined to have concordant non-odontogenic pain (from process outlined above) the practitioner's stated etiology of either "TMD" or "deafferentation pain" will be used to define the etiology for the non-odontogenic pain. Using threshold values of  $\geq 3$  for the TMD Screener and  $\geq 3$  for the PDAP Screener, the prevalence of TMD Screener- and PDAP Screener-related persistent pain at 6- and 12-months for all patients will be calculated and described in a similar fashion as listed above (i.e., proportions, 95% CIs, mean, median, range by groups).

5) Functional status, using JFLS, and health-related quality of life, using EQ5D5L, will be calculated for all patients and described in a similar fashion as listed above (i.e., proportions, 95% CIs, mean, median, range by groups). Student's t-test will be used to compare the mean values between groups, such as persistent pain vs. no persistent pain, non-odontogenic pain vs. odontogenic pain, and TMD vs. PDAP. Adjustment for differences at baseline will be performed. Some missing data at follow-up is expected. If only a small number of patients have missing data, we will limit the analysis to responders. If the percent is deemed substantial enough to affect outcome analyses, we will use standard multiple imputation methods to estimate missing data.

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

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

The following will be considered source documents and maintained by HP IDCC via electronic data management system:

- Screening Criteria Log
- Patient Contact Form
- Patient Before-Treatment Questionnaire
- Patient After-Treatment Questionnaire
- Patient 1-Week Questionnaire
- Patient 6-Month Questionnaire
- Patient 12-Month Questionnaire
- Practitioner Before-Treatment Questionnaire
- Practitioner After-Treatment Questionnaire
- Practitioner 12-Month Questionnaire
- Patient Radiographs before and after treatment and at 12 months
- Radiograph Interpretation Form

All study source documents must be maintained in a secure manner, and authorized practice or HP IDCC personnel will have access to the source documents stated above.



## **12 QUALITY CONTROL AND QUALITY ASSURANCE**

For the quality management activities associated with data collection and processing, the HP IDCC will develop a data management plan which will detail quality management procedures including the development of data quality checks in the database system and the processes related to the manual review of data, discrepancy management, delinquent data handling, data updates, data verification and approval, and database audit.

The online questionnaires are designed with data validation checks. If out of range values are entered by the patient or provider, the individual will be alerted and asked to provide a value that is in range. Patients who move on to telephone follow-up will interact with a trained telephone interviewer from the HP IDCC. This interviewer will complete the interview, and questionnaire responses will be entered directly into the electronic system via the HP IDCC telephone interviewer interface. Data will be entered in real-time and will be subject to the same quality checks as the study participant interface. If the patient refuses to answer a question, this is noted in the online system by the interviewer. A subset of patient telephone interviews will be monitored by HP IDCC supervisory staff. 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 Statistician. The datasets will be provided to the Statistician via secure data transfer method.

## 13 ETHICS/PROTECTION OF HUMAN SUBJECTS

### 13.1 Ethical Standard

The SPIs, GPI, and practitioners 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.

### 13.2 Institutional Review Board

This protocol will be reviewed by the National Dental PBRN Central Institutional Review Board (CIRB). The UAB-IRB for Human Use serves as the National Dental PBRN CIRB.

Local institutions have the prerogative to use the National Dental PBRN CIRB review or conduct their own local review. If the RAS or other local institution decides to use the National Dental PBRN CIRB review, the National Dental PBRN CIRB is responsible for the review of the protocol. The National Dental PBRN CIRB then performs all future continuing protocol reviews and amendment (new protocol version) reviews. The CIRB also reviews unanticipated problems distributed by the Administrative Unit to local institution PIs.

If a RAS or other local institution elects not to use the National Dental PBRN CIRB, the protocol, consent form(s) if warranted, recruitment materials and all participant materials will be submitted to the RAS or other institution IRB for review and approval.

Approval (either centrally for those regions who agree to central approval, or regionally for those who do not) 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.

### 13.3 Informed Consent Process

**Practitioners:** Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. The practitioner consent process is executed according to regional IRB requirements by the RCs, utilizing the general process described below for patients. Consent procedures will be administered prior to performing any study-related assessments or procedures. Practitioners may withdraw consent at any time throughout the course of the study.

**Patients:** Participating practices will designate who will execute consent procedures for the study. In most cases this will be the participating dentist. Any personnel who will be assigned to obtain consent will be defined as study personnel and must complete

required IRB training. Consent procedures will be administered prior to performing any study-related assessments or procedures.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study, and is based on regional IRB requirements; it continues throughout study participation. The patient's consenting process will be initiated via the tablet, pursuant to the overseeing IRB requirements. The practitioner or designee will explain the research study to the patient, answer any questions that may arise, and discuss risks and possible benefits of study participation, if applicable. If required by the responsible IRB, an electronic or paper consent form describing in detail the study procedures and risks will be given to the patient to read and review the document or have the document read to him or her. The participant will sign the consent document or give verbal approval of the consent process (depending upon central or regional IRB requirements), and a copy of the consent document will be emailed or given to the patient for his/her records if applicable. The consent process will be documented in the research record. Patients may withdraw consent at any time throughout the course of the study.

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

Children, defined as younger than 19 years, are excluded in this study because they have fewer permanent teeth, low treatment need for RCT, have not undergone reliability testing for the measures, and are rarely seen in dental clinics for evaluation of RCT-related tooth pain. Racial and ethnic minorities will be included in this study at least proportional to the composition in the dentist's patient population. Individuals of any gender group may participate as well.

#### **13.5 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.

The security features of the data capture system will enforce strict limits on data access for various members of the team. The system will be configured to give study personnel "minimum necessary" access to data given the role of the person on the project.

## **14 DATA HANDLING AND RECORD KEEPING**

Only study personnel (*i.e.*, GPI, SPIs, co-investigators, study statistician, study epidemiologist, RCs, and HP IDCC personnel) and clinical site monitors will have access to the study data elements in the study database as described in Section 14.3 Types of Data. All study personnel will have completed the required training elements for human subjects research certification.

### **14.1 Data Management Responsibilities**

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the SPIs. The HP IDCC will maintain the electronic data capture system (EDC) and will provide support and processes to allow for accuracy and completeness of data collected. All source documents must be reviewed by the HP IDCC staff, who will ensure that they are complete. UPs must be reviewed by the SPIs.

Practitioners will be trained on the EDC by RCs prior to patient enrollment. Practitioners will provide questionnaire responses directly into the EDC system on a study-issued tablet and/or personal computer or smart-phone. Patients will be enrolled into the system at point of care, will provide consent and will provide data directly into the EDC system or via phone questionnaire. In the case of phone questionnaire, HP IDCC staff will enter data in real time into the EDC system. The HP IDCC staff will ensure that discrepancies generated by the system are resolved in a timely manner. The RAS staff will work with practitioners and/or patients to clarify any data issues and maintain a tracking log for the data changes.

### **14.2 Data Capture Methods**

Study specific questionnaires will be developed to include fields for all data elements required for participant assessments. The questionnaires are translated into a secure EDC system, which will be used to obtain data from participating practitioners and patients electronically before and after treatment and at follow-up. The EDC system will also allow for digital radiograph upload. An electronic (internet-based) data collection system will assist in ensuring that all required data 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 fields in the database will be programmed to allow only certain values and ranges so that data entered from the electronic system can be validated and data errors can be corrected. A similar database fully integrated into the online system will be used by HP IDCC telephone interviewers for those patients who undergo telephone follow-up and complete the questionnaires in that mode. For this situation, HP IDCC telephone interviewers will enter data into the EDC system and will respond to data queries generated by the EDC system. Reports and tools will be developed to help monitor the data activities.

Patients will be requested to submit 1 week, 6 month, and 12 month questionnaires within the study assessment windows. Reminders and other tools will be used to encourage timely submission of these assessments; however, it is expected that some patients will 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.

### **14.3 Types of Data**

Data for the present study consist of the following:

- Practitioner-level demographic data from the National Dental PBRN enrollment questionnaire
- Screening criteria log
- Practitioner-reported information in response to questions
- Patient-reported information in response to questions
- Radiographs and reviewer assessments

### **14.4 Schedule and Content of Reports**

Reports to monitor enrollment will be produced every 2 weeks during the participant enrollment period, until enrollment targets are attained and enrollment is closed and will be provided to the GPI, SPIs, study team and NIDCR. These reports will contain accrual information in aggregate and by important data variables of interest. These reports will also contain separate sections for each region.

The SPIs will send reports to the NIDCR Medical Monitor for review at six month intervals after study initiation until enrollment targets have been met, and then annually thereafter. Medical Monitor reports will include data regarding enrollment and retention, unanticipated problems and protocol deviations, primary outcome measures, quality management findings and other relevant parameters.

Reports to assess study retention will be produced every 2 weeks until data collection is complete and will be provided to the GPI, SPIs, study team and NIDCR. These reports will provide ongoing monitoring of participant retention. Retention data will be closely monitored overall, by region, and by practice, and futility analyses will be performed as needed. For patients who are lost to follow-up, reports to assess reasons for loss will be produced after data have 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 the study Data Management Plan developed by the Data Manager at HP IDCC. Briefly, the data will be locked and final datasets will be generated at the end of the study. Prior to locking the database, the HP IDCC Data Manager or designee will ensure all data are complete and clean and will obtain approval from the SPIs to proceed with the data lock. The date and time of database lock will be documented.

#### **14.5 Study Records Retention**

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

As outlined by IRB regulations, data will be destroyed in an appropriate and safe way no sooner than three years from the date that the grant FFR is submitted to the NIH and with the GPI and SPIs concurrence. The file connecting patients' names with their unique identification number will be kept in a password-protected file by the HP IDCC and on the GPI's computer for a minimum of three years from the date that the grant FFR is submitted to the NIH; after that time, and with the GPI and SPIs concurrence, it will be destroyed in accordance with IRB regulations.

#### **14.6 Protocol Deviations**

A protocol deviation (PD) is any noncompliance with the clinical study protocol. The noncompliance may be on the part of the patient, practitioner or office staff, study team members, or Network personnel. As a result of deviations, corrective actions may be developed by the study team and should be implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to NIDCR and the local IRB, according to their requirements.

Any protocol deviation that is reportable to an IRB must also be reported to NIDCR. NIDCR defers to the IRB for reporting time-frame requirements. Once a 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.

## 15 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>.

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## **SUPPLEMENTAL MATERIALS**

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

Appendix A: Schedule of Events

Appendix B: Patient Retention Plan

### APPENDIX A: Schedule of Events

	<b>Patient Enrollment</b> (visit 1; day 0)	<b>Before-Treatment</b> (visit 1a)	<b>After-Treatment</b> (visit 1b)	<b>1 Week*</b> (visit 2; day 7-14)	<b>6 Months*</b> (visit 3; day 180 +/-30)	<b>12 Months*</b> (visit 4; day 305-455)	Discontinuation and/or Withdrawal
Procedures							
Assessment of Eligibility Criteria	x						
Administration of Consent	x						
Patient Contact Information		x					
Patient Questionnaires (In-office)		x	x			x	
Patient Questionnaires (online/telephone)		X**	X**	x	x	x	
Practitioner Questionnaires		x	x				
Upload Radiographs(s)			x			x	
Radiograph Interpretation Form†			x			x	

\*Follow-up patient data collections will occur at 1 week, 6 months and 12 months after RCT completion.

Practitioner follow-up data collection will occur at 12 months.

\*\*The CC will follow-up with patients that do not complete the Before and/or After-Treatment Questionnaires in the office.

†Radiograph Interpretation Forms are completed by trained, blinded study staff.

## APPENDIX B: Patient Retention Plan

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

Retention of study patients 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 the type. The four types of retention issues are:

**Lost:** Patients move and their new location cannot be found.

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

**Refused:** Patients decide they no longer want to continue participating in study.

**Unable:** Patients no longer seeing their original/enrolling practitioner.

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

### Methods to Minimize “Lost”

- 1) At patient enrollment, emphasize study requirements to patients:
  - a. Patients are part of a 12 month longitudinal study, and the importance of follow-up questionnaires.
  - b. HP IDCC will contact patients for the completion of questionnaires.
  - c. Entry criteria will include the ability and likelihood of maintaining participation throughout the study.
  - d. Collect information on:
    - i. Home telephone number
    - ii. Cell phone number
    - iii. E-mail address
    - iv. Contact information (including cellular telephone and email) of one person, and for whom they give permission for us to contact that will know of the patient’s whereabouts.
  
- 2) At the end of the enrollment visit, confirm contact information (of patient and one additional contact person).

- 3) HP IDCC makes contact with study patients prior to the follow-up assessment due dates.
- 4) 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 HP IDCC to receive the patient contact information and the contact information of one person who does not live in the same household as the patient, to assist the HP IDCC in their follow-up with the study patient post baseline.
- 5) The process of contacting non-responder practitioners for the completion of the questionnaires will be attempted by the RCs after the Study Manager informs the RC which practitioners with whom to conduct reminders.
- 6) Number of Patients per Practitioner Considerations:  
Dentists will be asked to enroll approximately 7 patients, and endodontists will be asked to enroll approximately 18 patients (the approximate maximum for any one dentist or endodontist is 50) in an approximate 10-14 week timeframe during the enrollment period.
- 7) Given the above design features, patients should not be “lost”. However, if a patient moves and contact is lost, the HP IDCC will implement tracing procedures.

#### Methods to Minimize “Missing Data”

- 1) Within the enrollment period, dentists will be asked to enroll approximately 7 patients and endodontists will be asked to enroll approximately 18 patients (the approximate maximum for any one dentist or endodontist is 50) in an approximate 10-14 week timeframe. Patients will be asked to complete their questionnaires before and after treatment, 1 week, 6 months, and 12 month post baseline visit.
- 2) Ask participating offices to develop a system to flag records of patients in their practices who are participating in the study, as well as to flag study patients in the office schedule. In this way, study personnel will be alerted to the fact that the patient is at the office. Flagging the patients in the schedule will help to ensure that patients are not inadvertently scheduled when the practitioner will not be in the office.

- 3) 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 patients 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 patients who refuse to continue participating. At enrollment, patients are informed that they are agreeing/consenting to participate in a longitudinal study. Patients who enroll are required to state a willingness to participate throughout the study.

### Methods to Minimize “Unable”

- 1) There are several scenarios in which a patient stops seeing the original/enrolling practitioner:
  - a. Patient does not move, but:
    - i. changes dentists in the same practice
    - ii. changes dentists in a different practice
    - iii. stops seeing any dentist
  - b. Subject moves
    - i. sees new dentist
    - ii. stops seeing any dentist
  - c. Dentist retires or dies
  - d. Dentist moves
  - e. Dentist refuses to continue participating
- 2) The operational impact of all of the above scenarios can be summarized by two scenarios:
  - a. Patient has a new dentist (not a National Dental PBRN member)
  - b. Patient stops seeing any dentist
- 3) Locating the patient should not be a problem (see Methods to Minimize “Lost”), and having the patient agree to continue participating should not be a problem (see Methods to Minimize “Refused”).

### Other Administrative and Design Methods to Increase Retention Rates

- 1) IRB/Informed Consent Considerations to Reduce Attrition

- a. Incorporate permission into the ICF for all relevant study personnel to contact the patient. This will allow all communications with the patient by study personnel without having to involve the dental office.
- 2) Financial, but non-coercive, incentive to patients to encourage continuing participation.

#### Additional Methods for Patients Who Have Missed a Follow-up Assessment

- 1) Prior to the follow-up interval, the HP IDCC will use the confirmed contact information to contact the patient by email to remind the patient to complete the study questionnaire.
- 2) If successful in contacting the patient, there will be special emphasis on reminding the patient of the importance of his/her participation in the study and the importance of complying with the study follow-up questionnaires.
- 3) If the patient cannot be reached, the person designated as an additional connection to the patient will be contacted to confirm the patient's contact information and/or determine the patient's whereabouts and additional attempts will be made to make contact with the patient.
- 4) If the designee cannot be contacted, HP IDCC tracing resources will be used in an attempt to locate the patient for completion of the assessment.