

# **Cracked Tooth Registry**

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## **STATEMENT OF COMPLIANCE**

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

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## SIGNATURE PAGE

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

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The signature below constitutes:

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

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## LIST OF ABBREVIATIONS

CC	Coordinating Center
CEJ	Cemento-Enamel Junction
CFR	Code of Federal Regulations
Co-I	Co-Investigator
CRF	Case Report Form
CTS	Cracked Tooth Syndrome
DSMB	Data and Safety Monitoring Board
EC	Executive Committee
EPT	Electric Pulp Tester
FAQ	Frequently Asked Questions
FFR	Federal Financial Report
GPI	Grant Principal Investigator
IRB	Institutional Review Board
MOD	Mesial - Occlusal – Distal ( <i>the biting surface as well as the surfaces that contact the teeth on either side</i> )
MOP	Manual of Procedures
NCCL	Non-carious cervical lesions
NW PRECEDENT	Northwest Practice-based Research Collaborative in Evidence-based DENTistry
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
OHSU PROH	Oregon Health & Science University Practice-based Research in Oral Health (PROH) network
PBRN	Practice-Based Research Network
QA	Quality Assurance
QC	Quality Control
SPI	Study Principal Investigator
RAS	Regional Administrative Site
RC	Regional Coordinator
RCT	Root canal treatment
SAE	Serious Adverse Event/Serious Adverse Experience
US	United States



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## PROTOCOL SUMMARY

**Title:** Cracked Tooth Registry

**Précis:** This will be a prospective, observational 4-year cohort study of both symptomatic and asymptomatic cracked teeth in 3,000 patients from 150-300 National Dental Practice-based Research Network (National Dental PBRN) practices. Subjects will receive patient-, tooth- and crack-level assessments of a cracked tooth at baseline and follow-up visits over the subsequent four years. The association among characteristics, e.g., whether or not symptomatic, will be assessed in bivariate analyses, then generalized linear models will be used to adjust for patient clustering within practices, and stepwise regression will be used to build models. Time to specific outcomes will be compared for different treatment recommendations using Cox proportional hazards modeling.

**Objectives:** *Primary:* The primary objective of the study is to identify patient-, tooth-, and crack-level characteristics associated with initial tooth symptom status, and to determine, over a four-year follow-up period, the associations of these multi-level factors with changes (tooth “failure”) that may occur in an initially symptomatic or asymptomatic cracked tooth. Changes in the study tooth over time—outcomes that define the development of tooth “failure”—include crack progression, sign/symptom development, need for restorative dentistry, endodontic therapy or tooth extraction, development of periradicular lucency, and loss of pulp vitality.

*Secondary:* It is anticipated that many teeth will require treatment over the course of the study period. Therefore, secondary objectives of the study are to:

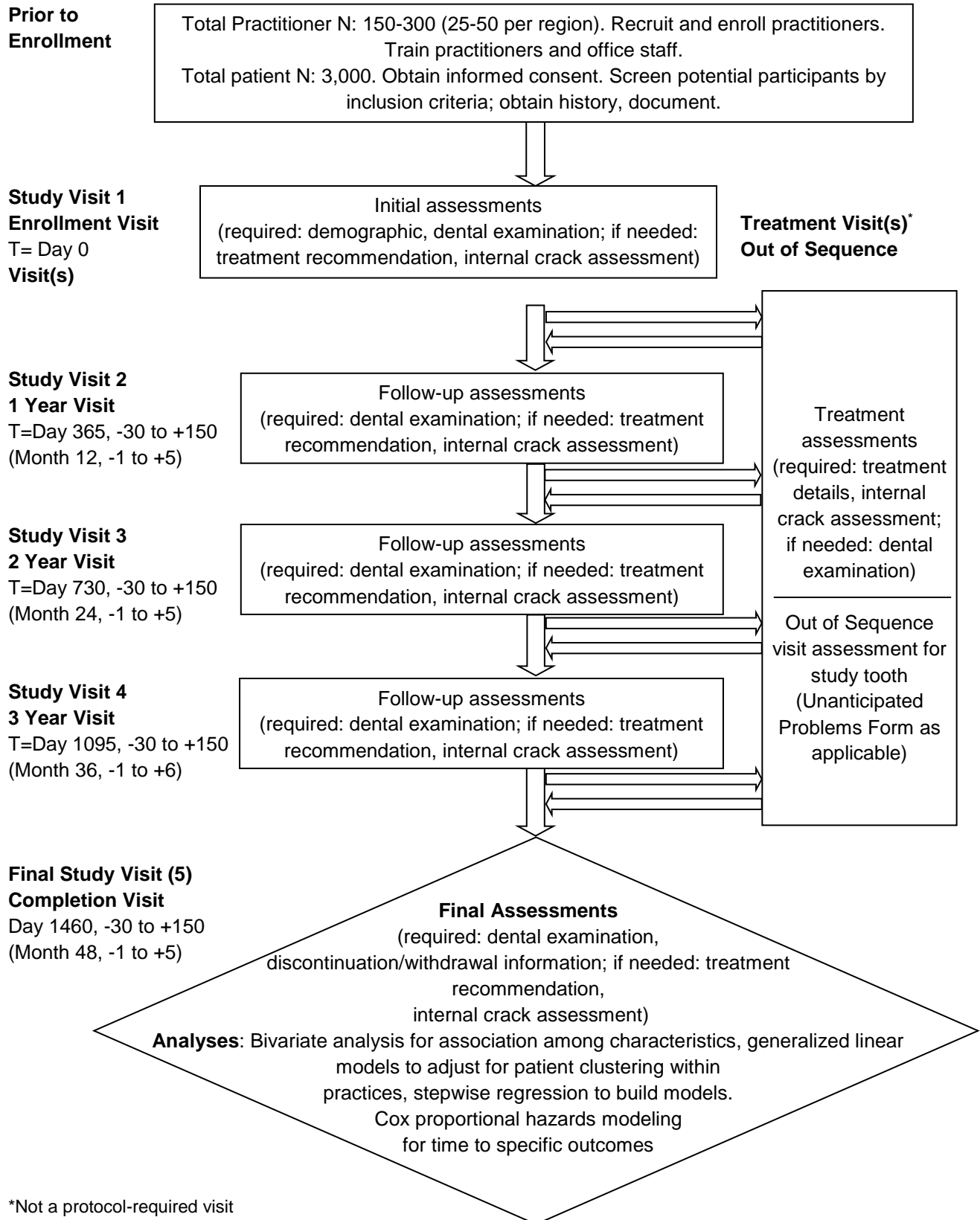
- (1) Identify multi-level (practice-, practitioner-, patient-, tooth-, and crack-level) factors associated with treatment recommendations for asymptomatic and symptomatic teeth provided by practitioners across the US;
- (2) Identify associations between crack characteristics and time-to-treatment rendered during the four-year follow-up period;
- (3) Determine, among treated cracked teeth, associations between the external and internal crack characteristics,

which will include externally detectable characteristics and internal characteristics that are observed during invasive treatment of the tooth; and

- (4) Evaluate outcomes of various treatments rendered on cracked teeth by determining associations between treatment rendered and time to tooth failure after treatment has been rendered on cracked teeth during the four-year follow-up period. These tooth outcomes include crack progression, sign/symptom development, and further recommended treatment of the tooth, development of periradicular lucency, and loss of pulp vitality.

<b>Population:</b>	The study will include approximately 3,000 adult patients 19 to 85 years old from National Dental PBRN practices with gender and demographic groups representative of the practice populations.
<b>Number of Sites:</b>	Approximately 150-300 National Dental PBRN practices
<b>Study Duration:</b>	72 months
<b>Subject Participation Duration:</b>	53 months
<b>Estimated Time to Complete Enrollment:</b>	10 months

**Schematic of Study Design:**



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## **2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE**

### **2.1 Background Information**

Cracked tooth syndrome (CTS) is a term applied to a presumptive diagnosis of incomplete tooth fracture that typically presents with consistent symptoms of pain to biting and temperature stimuli, especially cold. An incomplete tooth fracture is a source of pain and impaired function for patients and one that presents diagnostic and restorative problems to the dentist (Cameron, 1964). A patient survey of over 14,000 molars by the Oregon Health & Science University Practice-based Research in Oral Health (PROH) network revealed that nearly 70% of patients had at least one cracked molar. Since the outcomes for teeth with an incomplete tooth fracture can be so consequential, resulting in the need for major restoration, root canal therapy (RCT), or extraction, the development of a crack poses a significant problem to patients and dentists.

There is limited evidence regarding the best way of identifying risk factors for cracked tooth and regarding best practices for prevention, diagnosis, and treatment. Diverse therapies have been advocated and have shown some success, but these have mainly been based on a limited number of case reports and personal observations by clinicians. Further research is needed to support an evidence-based identification and treatment strategy for cracked teeth. This study proposes to develop a Cracked Teeth Registry to help meet the need for a more evidence-based, real-world approach to obtain diagnosis and treatment data from patients with cracked teeth visiting a private dental practice. In addition, the Registry will provide multiple communication and dental education opportunities for private practitioners interested in learning more about the diagnosis and treatment of cracked teeth.

Most of the studies reporting on the incidence and prevalence of incomplete tooth fractures have agreed that cracked teeth were significantly associated with intracoronal restorations and were prevalent in mandibular molars (Cameron, 1964; Cameron, 1976; Eakle et al, 1986; Gher et al, 1987). The types of restorations most associated with cracks were type I or type II mesial-occlusal-distal (MOD), and a direct relationship between the size of the restoration and the occurrence of a crack has been reported (Cameron, 1976; Eakle et al, 1986; Gher et al, 1987; Chong, 1989). The highest prevalence rates appeared in patients over 40 years old (Cameron, 1964; Roh et al, 2006; Cameron, 1976; Eakle et al, 1986). While earlier studies showed women being more affected than men (Cameron, 1964; Cameron, 1976), one recent study showed an almost equal distribution between gender groups (Roh et al, 2006). Bader et al (Bader et al, 1995) reported on the overall incidence rates of complete tooth fractures. The complete fracture rates were 5.0 per 100 for all teeth and 4.4 for posterior teeth, with 15% of fractures resulting in pulpal involvement or extraction. The corresponding rates for molars and premolars were 3.1 and 1.3 teeth per 100 adults, respectively, from the total number of fractures seen in posterior teeth. Recent research has shown that cracks in teeth with no restorations appear more frequently than previously thought, and the location of cracked teeth is highly variable (Roh et al, 2006).

A review of the studies reporting on the risk factors for cracked teeth draws attention to the multifactorial aspect of the cracked teeth etiology, with two factors being considered as predisposing factors for cracked teeth: natural predisposing factors (lingual inclination of the lingual cusps of mandibular molars and steep cusp/deep fossa of maxillary premolars, bruxism, clenching, extensive attrition, and abrasion) and iatrogenic factors (use of rotary instruments, cavity preparation, and the width and depth of the cavity) (Geurtsen et al, 1999; Lynch et al, 2002). However, the most commonly identified etiologic factors for cracks or incomplete tooth fractures were the presence and the design of cavity preparations (Ratcliff et al, 2001; Bader et al, 2004). Large restorations, improper and overzealous preparations, the inappropriate use of pins, and marginal ridge restorations also were mentioned as factors responsible for cracked teeth (Dilts et al, 1970; Mondelli et al, 1980). Many other factors, such as the size and shape of the cavity and isthmus (Mondelli et al, 1980; Re et al, 1981; Eakle et al, 1985), the type of restorative material (amalgam, composite, ceramic) or the restorative technique (bonded vs. unbonded, incremental vs. bulk filling techniques) (Bremer et al, 2001; Reel et al, 1989; Gelb et al, 1986; Franchi et al, 1999; Santos et al, 2005; Wiczokowski et al, 1998) seemed to play a role in the fracture strength of the restored teeth. Masticatory forces, parafunctional activities, excursive interferences, morphological aspect of the tooth, thermal fluctuations, and age were also considered in the etiology of cracked teeth (Ratcliff et al, 2001; Lynch et al, 2002; Geurtsen et al, 2003).

CTS has been described in the literature as a difficult diagnosis and a treatment problem (Cameron, 1964). The diagnosis of CTS in the past has been based exclusively on tooth symptomatology: localized pain during chewing or biting, unexplained sensitivity to cold, and pain on release of pressure (Cameron, 1964; Chong, 1989; Thomas, 1989; Geurtsen, 1992; Turp et al, 1996; Homewood, 1998; Davis et al, 1999; Ratcliff et al, 2001; Lynch et al, 2002; Griffin, 2006). Besides the symptomatology described by the patient, the diagnosis of CTS could be verified through a succession of procedures or tests performed by the clinician. Visual inspection, transillumination, and staining (Davis et al, 1999; Ailor, 2000; Wright et al, 2004), percussion, biting, and thermal pulp tests (Turp et al, 1996; Davis et al, 1999; Lynch et al, 2002), radiography (Ailor, 2000; Griffin, 2006), microscopy (14X-18X) (Clark et al, 2003), and ultrasound (Culjat, 2005) all have been suggested as having the potential to detect cracks within tooth structure. However, CTS may still be difficult to diagnose and may be a source of frustration for both the dentist and patient. None of the different diagnostic procedures suggested have been tested in a controlled clinical study.

Diverse therapies have been advocated for patients with cracked teeth, and a number of successful outcomes have been reported. However, successful results were mainly based on a limited number of case reports and personal observations by clinicians. The selected method of treatment for cracked teeth depended on the severity of symptoms, location of the crack, and the position of the tooth (Chong, 1989), and it was completed in two phases involving an initial stabilization followed by the permanent restoration of the tooth (Ailor, 2000).



For permanent restoration of teeth with cracks, both bonded and non-bonded amalgam and bonded resin composite have been mentioned in the literature for intracoronal restorations (Ailor, 2000; Davis et al, 1999; Geurtsen et al, 1999; Bearn et al, 1994; Trushkowsky, 1991; Opdam et al, 2003). Bonded complex amalgam restorations were preferred to non-bonded amalgam or posterior resin composite restorations in the treatment of fractured teeth (Davis et al, 1999; Bern et al, 1994). However, there has been little evidence regarding the efficacy of bonded amalgam or resin composite restorations with and without cuspal coverage in the treatment of painful, cracked teeth (Opdam et al, 2003; Silvestri et al, 1978).

More extensive treatments for a cracked tooth involved some form of protective coverage to bind the tooth together. Certain modifications of tooth preparation have been suggested (Casciari, 1999) to improve the prognosis of cracked teeth. Partial and complete tooth coverage have both been used (Silvestri et al, 1978; Geurtsen, 1992; Griffin, 2006; Ailor, 2000), but besides some isolated presentations of case reports, the literature does not provide information about clinical trials conducted to support the widespread use of extracoronal restorations in the treatment of cracked teeth.

Recent examinations of restored posterior teeth suggested that evaluation of crack growth due to cyclic loading might contribute to a greater understanding of restored tooth fractures. In restored teeth, fatigue and fatigue failures were expected to result from cyclic loads that were associated with typical oral activities (Arola et al, 2001; Arola et al, 1999; Shor et al, 2003; Arola et al, 2005; Bajaj et al, 2006; Franchi et al, 1999; Santos et al, 2005). Fracturing following the placement of restorations has been considered to be dependent on the type of material used for the initial repairs (i.e. reinforcement through composite or amalgam) (Arola et al, 2001), on the method of tooth preparation rather than restorative material (Arola et al, 1999; Arola et al, 2005), or on the age and hydration of the human dentin (Bajaj et al, 2006).

Recent studies by two separate practice-based research networks in the northwest U.S. have shown prevalence of individuals with at least one cracked molar to be 70% (OHSU PROH network) and individuals with at least one cracked posterior tooth to be 78% (Northwest PRECEDENT). Internal surveys of each network's members revealed that cracked teeth were the top priority of all research topics considered. Initial studies in both networks have provided valuable information on external crack characteristics and their relationship to symptoms and crack progression. Interestingly, it was found that in a mean follow-up of just 1.5 years, almost 10% of previously asymptomatic cracked teeth became symptomatic, and 25% of all cracked teeth showed some sign of crack progression, implying that earlier or more aggressive intervention may be appropriate. However, much of the information gathered in these earlier studies is incomplete or inadequate to fully characterize the implications of cracks in teeth, and much information remains to be garnered regarding the impact of various restorative treatments on cracked tooth longevity and performance.

## **2.2 Rationale**

The identification of factors that predict adverse outcomes in cracked teeth could help in developing a cracked tooth risk assessment system akin to existing caries risk

assessment tools. Therefore, this study will follow, on a national level, a large population of cracked teeth over an extended period of time, some of which will be treated and some of which will not be treated, using the data from earlier studies to refine specific evaluation characteristics.

We hypothesize that there are specific externally accessible characteristics of cracked teeth, that either individually or when combined, are predictive of adverse outcomes in those teeth and correlate with penetration of these cracks deeper into the tooth. A valuable aid to practitioners would be the ability to predict the likelihood of crack progression based on defined patient-, tooth- and crack-level traits, thereby providing an evidence-based approach as to when to intervene.

This study will also examine treatment recommendations and treatment outcomes for cracked teeth. We hypothesize that certain treatments will be more effective than others at stabilizing a cracked tooth from crack and/or symptom progression. The study will examine changes in cracked teeth before and after treatment to assess the effectiveness of various treatments. Data on the comparative effectiveness of various treatments for cracked teeth would provide evidence-based guidance on how and when to intervene.

Current practitioner philosophy and attitudes regarding cracked teeth not only determines their current treatment approach, but may also impact their receptivity to future evidence dissemination. The study will also gather information about the strategies practitioners use to determine timing and type of treatment for cracked teeth and will assess how treatment recommendations are associated with practitioner and practice characteristics. We hypothesize that treatment recommendations will vary by practice and practitioner characteristics.

## **2.3 Potential Risks and Benefits**

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

### **2.3.1 Potential Risks**

As with any study, there is the possibility of breach of confidentiality. Appropriate precautions will be taken and procedures will be followed to maintain confidentiality. These include use of unique study codes for participants, encryption of electronic data for transmission to the coordinating center, 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.

### **2.3.2 Potential Benefits**

Participation in the study would provide no direct benefit to participants. Benefits would accrue to society in that information regarding the fuller characterization of cracked

teeth, and the effectiveness of treatment outcomes, could enhance care for future patients through evidence-based recommendations for more timely and appropriate interventions.

### **3 OBJECTIVES**

#### **3.1 Study Objectives**

##### **3.1.1 Primary Objectives**

The primary objective of the study is to identify patient-, tooth-, and crack-level characteristics associated with initial tooth symptom status, and to determine, over a four-year follow-up period, the associations of these multi-level factors with changes (tooth “failure”) that may occur in an initially symptomatic or asymptomatic cracked tooth. Changes in the study tooth over time—outcomes that define the development of tooth “failure”—include crack progression, sign/symptom development, need for restorative dentistry, endodontic therapy or tooth extraction, development of periradicular lucency, and loss of pulp vitality.

##### **3.1.2 Secondary Objectives**

It is anticipated that many teeth will require treatment over the course of the study period. Therefore, secondary objectives of the study are to:

- (1) Identify multi-level (practice-, practitioner-, patient-, tooth-, and crack-level) factors associated with treatment recommendations for asymptomatic and symptomatic teeth provided by practitioners across the US;
- (2) Identify associations between crack characteristics and time-to-treatment rendered during the four-year follow-up period;
- (3) Determine, among treated cracked teeth, associations between the external and internal crack characteristics, which will include externally detectable characteristics and internal characteristics that are observed during invasive treatment of the tooth; and
- (4) Evaluate outcomes of various treatments rendered on cracked teeth by determining associations between treatment rendered and time to tooth failure after treatment has been rendered on cracked teeth during the four-year follow-up period. These tooth outcomes include crack progression, sign/symptom development, and further recommended treatment of the tooth, development of periradicular lucency, and loss of pulp vitality.

#### **3.2 Study Outcome Measures**

##### **3.2.1 Primary Outcome**

The primary outcomes for the study are the association of patient-, tooth- and crack-level characteristics noted at baseline with initial tooth symptom status in cracked teeth, and the association of patient-, tooth-, and crack-level characteristics with changes (tooth “failure”) over time in the cracked tooth that is followed in the study.

For each subject enrolled, only one cracked tooth will be followed, to minimize the time required for data collection for each subject.

### Patient-, Tooth- and Crack-level Characteristics

The following patient-, tooth- and crack-level characteristics will be assessed at baseline, and/or at the time of any cracked tooth treatment and/or at annual follow-ups for four years:

Patient characteristics: demographics (age, race, ethnicity, sex, education, dental insurance status), type and duration of patient-reported symptoms and/or dentist assessed signs (spontaneous pain, biting pain, cold pain), and patient habits (e.g., night/day bruxism, clenching, holding between teeth or bite objects, unilateral chewing).

Tooth characteristics: number of cracks in study tooth, location of study tooth, wear facets through enamel, whether roots are exposed to oral cavity, presence of caries, location of restoration (if present) and material used, clinical acceptability of restoration, materials in occlusion with the tooth, and radiographic appearance (only if a radiograph was performed in the course of normal care).

Crack characteristics (assessed for multiple cracks, if present in the study tooth): tooth surfaces involved, crack direction, crack staining, crack connection with an existing restoration, crack intersection with other crack(s) (if present), whether the crack is tactilely detectable with an explorer, and whether the crack blocks light when the tooth is transilluminated.

### Tooth Symptom Status

Cracked tooth symptom status at baseline will be categorized as symptomatic or asymptomatic. Symptom status will be determined by type and duration of patient-reported symptoms and/or dentist-assessed signs (spontaneous pain, biting pain, cold pain).

### Changes in Cracked Tooth

Changes in the tooth that is identified at baseline will be assessed at each follow-up visit and will be labeled using the following tooth “failure” variables:

1. Crack progression, as evidenced by partial or complete tooth fracture: a partial tooth fracture is defined as the loss of a portion of tooth structure coronal to the periodontal attachment (e.g., loss of a cusp), while total tooth fracture refers to a fracture that includes both the coronal and radicular tooth structure below the periodontal attachment (e.g., a fracture that renders the tooth non-restorable). Crack progression can manifest in other ways as well, e.g., more cracks can appear, or an existing crack can lengthen, or an asymptomatic cracked tooth can become symptomatic.
2. Signs/symptom development: Signs and symptoms of CTS (pain associated with biting, which may or may not be accompanied by pain to thermal stimuli) that develop

during the course of the study when none were present at the time of enrollment, or that worsen from baseline. Multiple dental maladies can cause pain to biting and/or thermal stimuli. It will be necessary for the dentist to differentiate among these as best as possible in order to collect valid data. A diagnosis of CTS will only be made if subjective (patient reported) and/or objective (dentist duplicated) biting pain is present. However, it will also be necessary to eliminate other sources of biting sensitivity (e.g., abscess) by verifying tooth vitality and/or lack of radiographic evidence of a periradicular lucency (as determined by routine dental care).

The following are surrogate measures of crack characteristics and/or crack progression that have resulted in a need for treatment to address the cracked tooth. Treatment may be indicated because of pain and/or tooth structural degradation that compromises the patient's oral health.

3. Restorative dentistry: Restoration of the tooth that includes a portion or all of the coronal tooth structure in order to address the signs and/or symptoms of a cracked tooth (e.g., a crown to reinforce weakened tooth structure or an onlay to replace a fractured cusp).
4. Endodontic therapy: Recommendation for biomechanical removal of the contents of the pulp chamber and pulp canal system and replacement with an obturation material.
5. Tooth extraction: Recommendation for complete removal of the study tooth. If the practitioner has recommended extraction, this will be counted as meeting the outcome variable, even if the patient has not yet completed treatment. This is the only outcome variable in which no further follow-up is required.
6. Periradicular lucency: A visually detectable loss of osseous radiodensity adjacent to the tooth root structure (This is a dichotomous - yes or no - variable). Radiographs will be taken as part of routine care and are not a requirement of the study.
7. Pulp vitality: Pulp vitality will be determined by the dentist with application of a cold stimulus. Practitioners will be asked to use refrigerant spray for cold vitality testing, but may apply other cold vitality testing (e.g., ice) if refrigerant spray is not available. Practitioners may use electric pulp testing to determine pulp vitality if they are uncertain of the results from the cold test or do not have other means for pulp testing. Practitioners will be asked to use the same technique(s) throughout the study to ensure consistency among the evaluation periods (This is a dichotomous - yes or no - variable). Part of the follow-up data collection will be to ask the dentist to describe how they determined pulp vitality for the study tooth.

Another variable ("Any Outcome") will be derived and a treated (or untreated) cracked tooth will be labeled as this derived outcome variable if any of the listed variables are observed during the follow-up period.

### **3.2.2 Secondary Outcomes**

Practitioner characteristics (e.g., year of dental school graduation and gender) and practice characteristics, including practice setting and geographic region of practice, will be recorded and will be assessed with the patient-, tooth-, and crack-level

characteristics listed above to determine the association of these characteristics with treatment recommendations for cracked teeth. Treatment recommendations to address the needs of the subject teeth include recommendations for noninvasive treatment, restorative dentistry (intracoronal vs extracoronal restoration, bonded vs non-bonded restoration, type of material), endodontic therapy, extraction, or other.

Treatment rendered on study teeth will also be recorded, utilizing the same variables as for treatment recommendations listed above, to identify associations between crack characteristics and time-to-treatment rendered during the four-year follow-up period.

For those teeth that require invasive treatment (e.g., a subject tooth is prepared for a restoration), an assessment of the internal crack characteristics via practitioner observation will provide information on what external crack characteristics are associated with impingement of vital structures within the teeth (e.g., cracks that extend into dentin, below the Cemento-Enamel-Junction (CEJ) onto root structure, into the pulp). Associations between internal crack characteristics and external crack characteristics will be assessed.

To evaluate outcomes of treatments rendered on cracked teeth, the study cracked tooth will be assessed for tooth “failure” variables listed above.

## 4 STUDY DESIGN

### 4.1 Main Study

- This will be a prospective, observational 4-year cohort study of both symptomatic and asymptomatic cracked teeth. This research is a National Dental PBRN study, and consequently it is multicenter in that numerous dental practices will participate in the study procedures.
- The study population will consist of dental patients with a cracked tooth. Because factors associated with cracked tooth treatment recommendations are also being studied, the dental practitioners represent a second study population. It is anticipated that 150-300 dentist practitioners, or 25-50 in each of the six National Dental PBRN regions, will participate. Each practitioner will enroll 10-20 subjects, with an enrollment goal of 3000 adult subjects, each having one posterior symptomatic or asymptomatic cracked tooth followed in the study. It is more difficult to titrate an exact study subject enrollment for a practice-based study, particularly for one that is national in scale. Therefore, some flexibility in enrollment is necessary, and each region may enroll up to 550 subjects into the study. Potentially as many as the first twelve practitioners enrolled into the study will be asked to pilot the data collection process, including completing Case Report Forms (CRFs), and appropriate modifications will be made. The data collected during this pilot may be included in the final analysis.
- The prospective, observational study design will allow an opportunity to inform our knowledge of cracked teeth characteristics and progression. The study will assess characteristics of initially symptomatic and asymptomatic cracked teeth and will follow these teeth to record changes that occur over time, some of which will receive treatment and some of which will not receive treatment. The study will relate initial symptom status and changes over time to patient characteristics, tooth characteristics, and crack characteristics. Treatment that would occur in the normal course of practice for a cracked tooth will be recorded and followed longitudinally.
- Subjects will be assessed annually and will be followed for up to 4 years after enrollment to assess progression and treatment of cracked teeth. It is key that within each practice, the patient enrollment and thus the practitioner-specific patient recall periods be condensed as much as possible, and no more than an 8 week period, so that the practice can maintain its focus on data collection for this study. The entire enrollment period may take a maximum of ten months to complete for all six regions. A similar schedule will be followed to assess these patients at one-year routine intervals, and/or at the time of treatment, over the subsequent four years.
- Every attempt will be made to perform follow-up assessments within one month prior to 5 months after the annual targeted date. Follow-up visits from 11-17 months will be classified as “1 year follow-up”, 23 months to 29 months as “2 year follow-up”, etc.



## 4.2 Substudy

In highly computerized practices, staying within the computerized system for all forms of data capture, regardless of whether it is for clinical care or research, is an important improvement in workflow (Schleyer 2010). In addition, electronic capture of research data offers potential advantages with regard to reduced time and effort for data entry, increased speed of data transmission and reduction of possible inaccuracies resulting from the multiple data extraction/transcription/reentry steps common in paper-based management of research data. A recent study (Schleyer 2013) has shown that a significant percentage of DPBRN (now National Dental PBRN) practitioners would be favorably disposed towards an electronic data capture option.

Therefore, a supplemental study, intended to investigate electronic data collection in dental practice-based research, will be conducted in conjunction with the main cracked tooth study. Through a collaboration with the Regenstrief Institute, this substudy will evaluate the feasibility of utilizing an electronic method for capturing research data for the study. The substudy will be implemented during the first year of the main study (at the first subject recall visit), in a subset of participating dental practices that are highly computerized or paperless. In these practices, data collection methods will not use paper forms, but will use a custom electronic Case Report Form (eCRF) integrated into Eaglesoft or Dentrax (or both). In either system, the eCRF will replicate the paper form and will be implemented through an end-user accessible forms design tool that is a standard part of both systems. The Center for Dental Informatics will use state-of-the-art user-centered design methodologies to ensure that the eCRF works reliably and is error-free prior to deployment. It will work closely with the system vendor(s) to integrate appropriate data entry and validation functions. Electronic data capture will be offered as an option to offices that desire to use it. Careful screening will ensure that only offices with the technological capabilities and know-how will use the form at first. Once the approach is well-tested and validated, it will be offered more broadly throughout the study. Outcomes of interest in the sub-study include issues and problems with using the form, the completeness and accuracy of the data entered (possibly compared to parallel paper-based recording of data), attitudes and opinions of users about the process, and the potential for continuation of this data collection method after the current protocol term.

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## 5 STUDY ENROLLMENT AND WITHDRAWAL

### 5.1 Subject Inclusion Criteria

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

- Sufficiently stable patient population such that the practitioner estimates he/she can recruit 10-20 subjects within the enrollment period who will remain in the practice for the four-year study duration and can be relied upon to return for annual follow-up visits;
- Practitioner affirms that the practice can devote sufficient time in patient scheduling to allow focused recording of all data required for the study; and
- Practitioner does not anticipate retiring, selling the practice, or moving during the study.

The subject population will come from the National Dental PBRN practices participating in this study. Having a high subject recall rate is key to the success of this study. Therefore, a premium will be placed on selecting patients who not only meet the cracked tooth eligibility criteria (below), but who are considered to be reliable patients of record within the practice. Practitioners should only select patients to participate in the study if the patients have shown themselves to be regular attenders, who routinely present for annual recall visits.

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

- Adult between the ages of 19 and 85 years old;
- Has a posterior permanent natural vital tooth with a crack\*;
- The patient reasonably expects to remain in the geographic area for the following four years, and has a reasonable expectation of vitality for four years, i.e. the patient is available to remain in the study for full duration of the study;
- Willing to be contacted on a regular basis by any of these entities: the practice, Regional Coordinator (RC), and the Westat Coordinating Center (CC); and
- Willing to provide names and contact information for two individuals (friends or family members) residing outside of the patient's household. This information will be used for tracing and retention activities only.

\* The definition of what constitutes a crack is a key element to this study. The definition we will use is the following: An obvious break of the external contiguous structure of the tooth, but involves no loss of tooth structure (e.g., lost cusp). It has

been suggested that an external crack that blocks transilluminated light indicates that the crack extends into dentin. However, there are minimal data to support that concept. In light of this, along with the understanding that dentists have many and varying criteria for diagnosing cracks in teeth, this study will let dentists use their usual techniques to identify a cracked tooth, and record the criteria that allowed them to arrive at that diagnosis. In that way, transillumination will be a co-factor included in the analysis, allowing determination of the specific criteria that are most useful for crack diagnosis.

## **5.2 Subject Exclusion Criteria**

N/A

## **5.3 Strategies for Recruitment and Retention**

### **5.3.1 *Practitioner Recruitment***

We will need 150-300 dentist practitioners to participate, or 25-50 per region. This is based on the targeted enrollment of 3,000 subjects, each having one posterior symptomatic or asymptomatic cracked tooth. All National Dental PBRN dentist practitioners will be eligible to be approached for participation in the study. Dentist practitioners will be surveyed for interest in participating in the study. If more than 300 practitioners volunteer to participate, practitioners will be selected so as to provide a diverse practitioner population. The first priority will be to select practitioners on the basis of geographic region, with the goal of obtaining 25-50 practitioners per region. If more than 300 total practitioners and more than 50 practitioners in any region volunteer, additional criteria will be applied in the following priority: type of practice (private, public, HMO), location (urban, suburban, rural), practitioner experience (number of years from dental school graduation), practitioner gender, and practitioner age, to achieve a cohort of practitioners that is representative of the demographics for the National Dental PBRN practitioners within that region. We will rely on the RCs from the six regional administrative sites (RAS) to help recruit practitioners into the study. RCs are ‘the face of the nation’s network’, and many have strong, positive relationships with network members. Practitioners will be compensated for the time required to do the research, receiving \$50 for each baseline visit completed, \$25 for each annual recall visit completed, and \$25 for the first treatment visit for each patient. This first treatment can be provided at the baseline exam, annual visit, or out of sequence visit. Practitioners will be paid for only one (first) treatment visit per patient during the entire study period.

### **5.3.2 *Subject Recruitment***

We will attempt to enroll all 3,000 subjects in an approximate six-month period, but we realize it may take up to 10 months due to varying circumstances among the various regions and practices. To meet this subject recruitment goal, each participating dentist

practitioner will be asked to recruit 10-20 subjects. Practices should be able to meet the recruitment goal by enrolling at a rate of one patient per day and still fall within the 8 week or less enrollment period. However, practitioners may enroll subjects at a rate that best suits their practice situation. Specifically, the following decision rule will be implemented to determine the length of the enrollment period for a practitioner: The practitioner should stop enrolling patients after: 1) 8 weeks of attempting enrollment or 2) 20 patients are enrolled, whichever comes first. We will use a convenience sampling approach to enroll subjects into the research study, with an emphasis on enrolling the first 10-20 patients of the practitioners who meet the eligibility criteria.

Previous data from NW PRECEDENT have shown that approximately 11% of randomly selected patients will have a symptomatic cracked tooth (Hilton et al, 2012). Although we will not be randomly selecting subjects into the study, we will need to over-enroll (relative to a random sample) for symptomatic cracked teeth to allow us to compare and contrast crack characteristics between symptomatic and asymptomatic teeth. For the purposes of this study, a symptomatic cracked tooth is one with an external crack that also has symptoms (pain to cold or biting) not obviously attributable to other causes, e.g., caries, dentin hypersensitivity, occlusal trauma, leaking restoration. In addition, since previous research has shown that approximately 90% of symptomatic cracked teeth will be recommended for treatment (Hilton et al, 2011), overenrolling symptomatic cracked teeth will ensure that there is an adequate sample of cracked teeth that will receive treatment to allow internal crack characterization. We will attempt to have approximately one-third of the subjects (1,000) enrolled in the study with a symptomatic cracked tooth. We will ask that among the first 10 subjects enrolled, each practitioner attempt to have at least three subjects with a symptomatic cracked tooth. Likewise, we will ask that the same procedure be followed for the next 10 subjects of each practitioner. This will be a suggestion, not a requirement, as we want to ensure that practitioners have the latitude to enroll patients when it is most convenient for them to do so, given the workflow at the practice. However, once a practice has enrolled 14 asymptomatic subjects, that practice should only recruit symptomatic cracked teeth into the study.

Designated office personnel will introduce the study to patients who meet inclusion criteria when they are seen for a dental appointment. Any dental visit is eligible for patient recruitment at baseline, not just examination or recall visits. For patients who express interest in participating in the study, a designated individual will execute informed consent procedures with the patient. It is presumed that these patient recruitment tasks will be consolidated to one or two office personnel. However, each office should have the latitude to designate tasks that will work best within the normal operating procedures for their practice. Subjects will receive a \$25 gift card at the enrollment visit and for each study recall visit (maximum of five gift cards over the duration of the study). No patient remuneration will be given for data collection at interim assessment/treatment visits that occur between the regular enrollment/recall study visits. If a subject is discontinued from follow-up due to extraction of the study tooth, the subject will no longer be seen in the study and will not receive any additional gift cards after the tooth is extracted.

### **5.3.3 Subject Retention**

Subject retention is vital to this study, and Appendix E provides a subject retention plan for maximizing subject participation throughout the duration of the study. Subjects will be contacted by the practitioner's office at approximately the half-way point between annual recalls and reminded of the importance of their participation, and recall appointments will be made. Subjects will be contacted by the practitioner's office for recall reminders one to two months prior to their recall assessment. The general process for contacting patients for recall visits and reminders will be the same for each region; specifically, the practices will make the initial contact attempts. RCs will instruct the office to let them know if there has been no response from the initial recall attempts, and ask that the office do so within approximately 3 weeks of the attempt. The RC will then inform the CC, and the CC will initiate tracking procedures to identify updated patient contact information (detailed in MOP). Having the process start with the practitioner's office is important because the practices can ensure that the scheduling of study recall visits coincides with the periodic recall schedule of individual subjects as much as possible. However, the RC or CC will also be partners in making contact with the patient; examples of potential contact activities include sending out postcards or birthday cards as reminders. The RC or CC will make direct contact with the patient for visit scheduling and reminders when the practice is not able to do so. In addition, if an enrolled patient misses the recall window for a visit, additional steps will be taken to confirm his or her contact information prior to the next recall visit by initiating CC contact tracing procedures prior to the practice initiating contact attempts for recall visit scheduling and recall reminders.

## **5.4 Subject Withdrawal**

### **5.4.1 Reasons for Withdrawal**

Subjects are free to withdraw from participation in the study at any time upon request.

### **5.4.2 Handling of Subject Withdrawals**

In the case of subject withdrawal from the study, staff will only attempt continued follow-up data collection for subjects who are withdrawn due to an unanticipated problem. In those cases, only data related to the completion of reporting requirements for the unanticipated problem will be recorded. Subjects withdrawn from the study for any other reason will have the date and reason for withdraw recorded, but will not have any additional study data recorded. Although subjects withdrawn from the study may continue to receive normal clinical care as patients of the participating dentists, additional study data will not be collected from this continuing clinical care (except as noted above).

Replacement of subjects who withdraw or discontinue early will be allowed, but only during the initial subject enrollment period for each practitioner. The practitioner may

attempt to enroll one replacement subject for each subject enrolled who withdraws or discontinues during the practitioner-specific enrollment period.

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

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

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

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility. A power (sensitivity) analysis will be used to track whether loss to follow-up that will occur during the study jeopardizes the validity of the primary outcome measure.

## **6 STUDY SCHEDULE**

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

The study will proceed in stages: 1) each region will enroll 25-50 practitioners into the study; 2) practice personnel receive necessary IRB training and mail or in-person visits to have them sign practitioner informed consent forms (if required by that region's IRB), Individual Investigator Agreements, UAB Master Service Agreement, and similar documents; 3) RCs will ensure practices are trained in the appropriate study procedures (see below); 4) practices enroll subjects into the study. The CC along with the RAS and RCs will coordinate the launch of the study. Once the RC has trained an office in the practice procedures, that practice should begin recruiting subjects into the study immediately, or as soon as possible.

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

### **6.1 Screening**

A potential subject may be recruited at any dental visit, not just examination or recall visits. During the course of a dental visit, when it is determined that a patient has a symptomatic or asymptomatic cracked tooth and may be eligible for study participation, the designated office personnel will introduce the study to the patient and will ascertain that inclusion criteria are met. Enrollment and baseline examination may occur during the same dental visit at which eligibility was confirmed.

### **6.2 Enrollment/Baseline**

For patients who express interest in participating in the study, a designated office individual will execute the consent process with the patient and ensure that the consent document has been executed.

### **Enrollment/Baseline Visit (Visit 1, Day 0)**

- Obtain and document consent from participant.
- Obtain participant contact information and preferred method of contact (e.g., postal mail, email, telephone, text, other contacts); see Appendix E.
- Verify inclusion criteria.
- Record demographic information and results of dental examination.
- Record treatment recommendations, if applicable.
- Record internal crack assessment, if applicable.

### **6.3 Intermediate Visits**

#### **Visit 2, 1 Year Visit; Day 365, -30 to +150; Month 12, -1 to +5**

- Record results of dental examination.
- Record treatment recommendations, if applicable.
- Record internal crack assessment, if applicable.
- Verification of participant contact information and preferred method of contact.

#### **Visit 3, 2 Year Visit; Day 730, -30 to +150; Month 24, -1 to +5**

- Record results of dental examination.
- Record treatment recommendations, if applicable.
- Record internal crack assessment, if applicable.
- Verification of participant contact information and preferred method of contact.

#### **Visit 4, 3 Year Visit; Day 1095, -30 to +150; Month 36, -1 to +6**

- Record results of dental examination.
- Record treatment recommendations, if applicable.
- Record internal crack assessment, if applicable.
- Verification of participant contact information and preferred method of contact.



## **6.4 Study Completion Visit**

### **Visit 5, Completion Visit; Day 1460, -30 to +150; Month 48, -1 to +5**

**A final study visit may occur prior to day 1460, -30 to +150 (Month 48, -1 to +5) if the study tooth is extracted**

- Record treatment recommendations, if applicable.
- Record internal crack assessment, if applicable
- Record discontinuation/withdrawal information (see section 6.5 below).
- Record results of dental examination.

## **6.5 Withdrawal Visit**

- Record date and reason for withdrawal.
- Record other subject information only if withdrawal occurs at a study visit or out of sequence visit information, if consent was not withdrawn. Additional information recorded should only be that which is required for the visit type, as applicable (see above).

## **6.6 Out of Sequence Visit**

Information from out of sequence visits involving evaluation or treatment of the study tooth will be recorded.

Treatment visits:

- Record treatment details.
- Record results of internal crack examination after tooth preparation.
- If treatment was newly recommended since the last study visit, record results of dental examination and treatment recommendations.

Visits involving an unanticipated problem:

- Complete the NIDCR Unanticipated Problems (UP) Form.

## 7 STUDY PROCEDURES/EVALUATIONS

### 7.1 Study Procedures/Evaluations

Eligible and consented subjects will complete the Patient Characteristics CRF, which ascertains the baseline patient-level information detailed in section 3.2.1. Subjects will receive tooth- and crack-level assessment of a posterior tooth with an external crack at the Enrollment Visit (Baseline Exam & Treatment CRF) and annual recall visits (Annual Follow-Up Visit Exam & Treatment CRF). Diagnosis of cracks in teeth will be accomplished using visual inspection with magnification, transillumination, and tactile perception with an explorer; all of these criteria will be assessed and recorded for each crack. The practitioner must be able to visually detect evidence of a crack. Radiographic examination will be at the discretion of the practitioner.

If a study tooth receives treatment at the time of the baseline examination, Section 2 (Treatment Information) of the Baseline Exam & Treatment CRF will be completed. If a study tooth receives treatment at the time of an annual examination, Section 2 (Treatment Information) of the Annual Follow-Up Visit Exam & Treatment CRF will be completed. If a study tooth receives treatment at any time other than at the baseline or annual follow-up examination visit, including continuation of previous treatment, the Treatment Visit CRF will be completed. At the treatment-only visit, a detailed reassessment will be done only if there are adverse changes observed in the study tooth. Examples of such adverse changes include, but are not limited to the following:

- Longer duration of patient-reported symptoms associated with cracked tooth
- Worsening of dentist-assessed signs associated with cracked tooth
- Crack progression on cracked tooth, including fracture of tooth, as observed through visual inspection
- More cracks on cracked tooth as observed through visual inspection

If no adverse changes have occurred in the interim between the examination visit (baseline or annual) and the treatment visit, the reassessment would not need to be completed, as indicated by the skip pattern on the Treatment Visit CRF. If in doubt, the practitioner should complete the external crack assessment.

Only one cracked tooth will be enrolled per subject, so as to minimize the time required for data collection for each subject. Potential subjects will be evaluated to determine if they have an eligible posterior cracked tooth. If the patient has more than one eligible tooth, the following priority will be used to select the one tooth for enrollment:

1. Symptomatic tooth requiring treatment
2. Symptomatic tooth not requiring treatment
3. Asymptomatic tooth requiring treatment
4. Asymptomatic tooth not requiring treatment

If the subject has more than one eligible tooth at the highest priority level for which that patient meets the criteria, then the practitioner may use his/her discretion to select the subject tooth to be followed, with a preference for selecting the tooth that the

practitioner believes is most at risk for future treatment. In other words, if a patient has more than one symptomatic, vital tooth, then the practitioner should select the tooth most likely to require treatment sometime during the course of the study. These tooth selection criteria will maximize enrollment of symptomatic teeth and treated teeth.

Subjects with a study tooth that requires endodontic treatment or extraction should be treated or referred as the practitioner would normally manage the patient's care, regardless of whether or not the tooth is being followed in the study. Upon extraction, the study subject and tooth will be censored from further data collection. Upon completion of endodontic treatment, the practitioner should maintain the subject in the study and continue to follow the subject for the remaining study visits.

## **8 ASSESSMENT OF SAFETY**

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

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

#### **8.1.1 Unanticipated Problems**

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

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

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

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

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

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

## 8.2 Reporting Procedures

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

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

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

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

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

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

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

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

## **9 STUDY OVERSIGHT**

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

## **10 CLINICAL SITE MONITORING**

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. The network RAS will be responsible for clinical site monitoring for this study. RCs at each RAS will provide study training to practitioner sites and perform clinical site monitoring activities, to evaluate study processes and documentation based on NIDCR standards and principles of good clinical practice.

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

## 11 STATISTICAL CONSIDERATIONS

Statistical considerations, including sample size and power calculations, are further detailed in the Statistical Analysis Plan (SAP).

### 11.1 Study Hypotheses

Primary hypothesis: There are specific externally accessible characteristics of cracked teeth that, either individually or when combined, are predictive of adverse outcomes in those teeth.

Secondary hypotheses:

- Treatment recommendations will vary by practice and practitioner characteristics. It will be possible to consolidate practitioner’s varied philosophies regarding appropriate timing and type of treatment for cracked teeth into a few broad strategies.
- Specific externally detectable characteristics of cracked teeth correlate with penetration of these cracks deeper into the tooth.
- Certain treatments will be more effective than others at stabilizing a cracked tooth from crack and/or symptom progression.

### 11.2 Sample Size Considerations

All sample size estimates assume 80% power, significance level of 5%, and an intraclass correlation coefficient of 5%. The initial analysis will be baseline assessments comparing symptomatic to asymptomatic cracked teeth. Our target goal is to recruit 150-300 practitioners, each enrolling 10-20 patients. Below are possible scenarios for enrolling 3,000 cracked teeth.

practitioners	average number enrolled per practice		total number enrolled		overall total
	symptomatic	asymptomatic	symptomatic	asymptomatic	
300	3	7	900	2100	3000
250	4	8	1000	2000	3000
200	5	10	1000	2000	3000
150	7	13	1050	1950	3000

#### Power for baseline assessment

Using the 150 practitioners average 7 symptomatic and 13 asymptomatic cracked teeth per practice scenario (least powerful of above), if 20% of asymptomatic cracked teeth and 25.9% of symptomatic cracked have any specified characteristic or groups of characteristics, we will be able to detect this difference of 5.9% as significant. Thus, under various scenarios (namely, proportion with characteristic of interest), we will be able to detect differences as small as 5%-7% as significant.



### Power for follow-up assessment

For asymptomatic cracked teeth: Assuming 13 cases from each practice (6 or 7 in each of 2 groups [characteristic profile]), 1,950 cracked teeth for failure rates ranging from 10-50%, we will be able to detect differences in failure rates of 5% to 7% as significant in asymptomatic cracked teeth. For symptomatic cracked teeth: Assuming 7 cases from each practice (3 or 4 in each of 2 groups [characteristic profile]), 1,050 cracked teeth for failure rates ranging from 10-50%, we will be able to detect differences in failure rates of 6% to 9% as significant in symptomatic cracked teeth.

## **11.3 Final Analysis Plan**

All statistical analyses will be performed using SAS version 9.3.

### Analyses for Primary Objectives

#### (#1): Determine associations between patient-, tooth-, and crack-level characteristics and baseline tooth symptom status

Dependent variable: Tooth symptom status (see Section 3.2.1)

Independent variables: Patient-, tooth-, and crack-level characteristics (see Section 3.2.1)

Baseline data will be used to identify patient-, tooth-, and crack-level characteristics that are associated with the cracked tooth being “symptomatic”. Bivariate analyses will be performed examining the relationship of each patient-, tooth-, and crack-level characteristics with tooth symptom status using either chi-squared test for categorical data and t-test or Wilcoxon rank sum test for continuous data. Then, generalized linear models (outcome being tooth symptom status) will be used to adjust (variance and thus significance of differences) for patient clustering within practices. Patient-, tooth-, and crack-level characteristics will each be treated as separate domains; namely, a set of characteristics that best differentiates symptomatic from asymptomatic cracked teeth will be identified within each level [domain], then an overall model will be built. Stepwise regression will be used to build the models. Each characteristic with  $p < 0.1$  will be entered into the model, and those with  $p < 0.05$  will be retained. This approach will be used within level [domains] and then for the overall model.

#### (#2): Determine, over the four-year follow-up period, associations of patient-, tooth-, and crack-level characteristics with tooth “failure.”

Dependent variable: Tooth “failure” (see Section 3.2.1)

Independent variables: Patient-, tooth-, and crack-level characteristics (see Section 3.2.1)

Most of this analysis will be performed separately for asymptomatic and symptomatic cracked teeth at baseline, as development of symptoms is a “failure” (outcome) among asymptomatic cracked teeth.

The same analytic approach described above to identify predictors of symptomatic status will be used to identify predictors of failure, namely, the association of each patient-, tooth-, and crack-level characteristics with “failure” will be assessed first with bivariate analyses (e.g., chi-square, t-test, etc). Next, generalized linear models (outcome being tooth failure status) will be adjusted for clustering of patients within practices. Patient-, tooth-, and crack-level characteristics will each be treated as separate domains, as mentioned above, and a set of characteristics that best differentiates tooth failure/no failure will be identified within each domain, and then an overall model will be built. Stepwise regression will be used with the criteria described above to build a final model. Each characteristic with  $p < 0.1$  will be entered into the model, and those with  $p < 0.05$  will be retained. This approach will be used within level [domains] and then for the overall model.

Four-year tooth-failure probabilities will be produced for various subgroups based on tooth- and patient- characteristics for potential clinical application as an aid in treatment planning for cracked teeth.

#### Analyses for Secondary Objectives

(#1): Identify multi-level (practice-, practitioner-, patient-, tooth-, and crack-level) factors associated with treatment recommendations for symptomatic and asymptomatic teeth provided by practitioners across the U.S..

Dependent variable: Treatment recommendations (see Section 3.2.2)

Independent variables: Practice-, practitioner-, patient-, tooth-, and crack-level characteristics (see Section 3.2.2)

We expect to identify 3-6 treatment approaches that at least 80% of treatment recommendations can be grouped into. To evaluate associations of practice-, practitioner-, patient-, tooth- and crack-level characteristics with treatment recommendations, we will first use bivariate analyses examining multi-level characteristics with treatment recommendations, then multinomial regression to identify independent associations. These will be further refined by adjusting for or stratifying on select crack characteristics.

(#2): Identify associations between crack characteristics and time-to-treatment rendered during the four-year follow-up period.

Dependent variable: Time to treatment rendered (see Section 3.2.2)

Independent variables: internal and external crack characteristics (see Section 3.2.2)

Among cracked teeth, whether initially asymptomatic or symptomatic, we will examine time to treatment rendered, e.g., restorative, endodontics, or extraction, using Cox proportional hazards modeling. Cracked teeth with similar characteristics will be grouped together.

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(#3) Determine associations between external and internal crack characteristics (among treated cracked teeth)

Dependent variable: Internal crack characteristics (see Section 3.2.2)

Independent variable: External crack characteristics (see Section 3.2.2)

Analyses to correlate internal and external crack characteristics in cracked teeth will be restricted to teeth treated restoratively after study entry, an estimated 30% of cracked teeth (estimated n=900 at baseline). The relationship between external crack characteristics and internal characteristics will first be assessed with bivariate analyses. Next, variance (significance) will be adjusted for clustering of patients using generalized linear models. Then a final model will be built using stepwise regression in which the external crack characteristics with a  $p < 0.1$  in bivariate (cluster adjusted) analysis will be entered into the model and those with  $p < 0.05$  will be retained.

(#4): Evaluate outcomes of various treatments rendered on cracked teeth by determining associations between treatment rendered and time to tooth failure after treatment has been rendered on cracked teeth during the four-year follow-up period.

Dependent variable: Tooth "failure" (see Section 3.2.2)

Independent variable: Treatment rendered (see Section 3.2.2)

To evaluate outcomes of various treatments rendered on cracked teeth, cracked teeth with similar characteristics, namely, the surfaces involved, direction, staining, whether connects with restoration, and whether interacts with other cracks, will be grouped together. Time to specific outcomes, e.g., development of pain in initially asymptomatic cracked teeth, or other symptom progression, will be compared for different treatments rendered using Cox proportional hazards modeling. Models will be adjusted for tooth and patient characteristics that predict failure.

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

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

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

The following CRFs or portions of CRFs will be considered source documents, as it is not expected that all patients' clinical charts would contain the exact information collected on these CRFs: Study tooth characteristics, internal crack assessment after tooth preparation; questions on ethnicity, race, and highest level of education from the Patient Demographics CRF.

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

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

For the Quality Assurance (QA)/Quality Control (QC) activities associated with data collection and processing, the CC will develop a data management plan in which the specific data QA/QC procedures will be provided. The procedures will include the development of automatic data quality checks in the database system and the processes related to the data manual review, discrepancy management, delinquent data handling, data updates, data verification and approval, and database audit. A work instruction will be provided to the RCs at the RAS with the specified tasks, timelines of completing the tasks, roles, and responsibilities. The Data Manager at the CC will work with the RCs to ensure that all procedures are followed and that the data are checked according to the validation requirements specified from the study protocol. The RCs will perform QA review of a percentage of CRFs, as specified in the data management plan. In these QA reviews, data entered into the web-based system will be compared against CRFs. Mismatches will be corrected in the web system. At the end of the study, the RCs will ensure that all data collected by the regional offices are entered and cleaned. The Data Manager at the CC will verify the completion of data entry and clarifications by running monitoring reports. Once confirmed that the data entry are complete and the data are verified and approved for accuracy, the database will be locked for final analysis. During the study period, when interim data analysis is needed, the Data Manager will coordinate the activities with the RCs and the Statistician. The interim datasets will be provided with the data collected as of the specified date. The data in those datasets will be cleaned if possible but may contain pending issues which will be provided to the Statistician if requested. The datasets will be provided to the Statistician via secure data transfer method. The Quality Management Plan is detailed in Appendix G.

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

### **14.1 Ethical Standard**

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

### **14.2 Institutional Review Board**

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

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

### **14.3 Informed Consent Process**

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. If required by the responsible IRB, a consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The timing for the signing of the consent form required by the responsible IRB will be adhered to if written consent is required (i.e. before or after other study procedures). Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare

of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

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

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

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

Minors will be excluded because only permanent teeth are of interest, so to ensure that enrolled teeth can remain for the duration of the study.

#### **14.5 Participant Confidentiality**

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

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

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

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

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

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

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

### **15.1 Data Management Responsibilities**

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

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

### **15.2 Data Capture Methods**

Study-specific paper CRFs will be developed to include fields for all data elements required for participant assessments. A Web-based data collection system will ensure 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 field in the database will be programmed to allow only certain values and ranges so that data entered from the web system can be validated and data errors be corrected. Reports and tools will be developed to help monitor the visit and data activities. The reports with the summary of the data completion at enrollment and follow-up by the practitioners will be made available on the network web site.



After the paper data collection has been completed for a participant at enrollment and at each follow-up visit, the study materials for the participant may be placed in the participant's research file, which may or may not be kept separate from the regular dental charts. The participant log will be consulted to obtain the name of the patient corresponding to the study ID number printed on the CRF so that the dentist can cross-check information on the study form with the patient's dental chart. Questions about the data will be resolved by conferring with the staff member(s) who completed the CRF. After the dentist signs the CRF (if necessary), the designated staff member will transmit the data to RCs. The trained staff at the RAS will enter the data into the study database by logging into their account with the online data capture system. RAS staff members will respond to data queries generated by the data capture system and will have access to support staff at the CC if they need assistance with data processing.

If the substudy is implemented and the data from the substudy need to be loaded into the main study database, the CC will collaborate with the Regenrief Institute to develop a data transfer plan. The plan will provide detailed procedures, including how data will be extracted from Eaglesoft or Dentrax system, transferred to the CC, and loaded into the main study database. The loaded data will be reconciled with the electronic CRFs that were previously recorded in the database from the paper CRFs. The reconciliation results will be reviewed to assess the completeness and accuracy of the data collection in the substudy and evaluate the computerized or paperless data collection approach in those systems.

### **15.3 Types of Data**

Data for the present study consist of the following:

- Practitioner level data from the enrollment questionnaire;
- Patient-, tooth-, and crack-level assessments; and
- Unanticipated problems data (collected in the main study database).

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

Reports to monitor enrollment will be produced every two weeks during the participant enrollment period, until enrollment targets are attained and enrollment is closed. These reports will contain a section for accrual information in aggregate, with information on accrual of participants according to key characteristics (symptomatic vs. asymptomatic) cross-tabulated with treatment recommendation (Yes vs. No). These reports will also contain separate sections for each region, with information regarding participant accrual by site.

Reports to the DSMB will be produced at least annually, and may be produced more frequently at the request of the DSMB. As noted in Section 9 Study Oversight, most

data elements for inclusion in the DSMB reports will be clearly defined at the organizational meeting of the DSMB.

Reports to assess study retention will be produced every two weeks during each annual follow-up period. Retention reports will also be generated for DSMB reviews regardless of the annual follow-up period. These reports will provide ongoing monitoring of participant retention. Retention data will be closely monitored, and futility analyses will be performed as needed. In addition, a report will be produced for each individual practice that includes the practice's attrition rate and a comparison to the overall attrition rate for the study. These reports will be made available to the practitioners.

Reports to assess study progress will be produced annually, after the end of the data collection period for the enrollment visit and after the data collection period for each study follow-up visit. The study progress reports will contain frequencies and descriptive statistics for key questions from each study CRF. The identification of key questions will be determined by the SPI and other study team members. For subjects who are lost to follow-up, reports to assess reasons for loss will be produced after data has been obtained following the data collection period for each study follow-up visit.

As portions of the study objectives can be addressed through analyses of baseline data only, it is anticipated that some full analysis can begin after baseline data collection is complete. Interim analysis reports that address objectives requiring all study data to be collected will be produced at the discretion of the CC Statistician, in consultation with the SPI, and other study team members. The content of these reports will be determined by the CC Statistician, in consultation with the SPI, and other study team members.

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

No masking or coding is anticipated for this study.

## **15.5 Study Records Retention**

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

As outlined by IRB regulations, data will be destroyed in an appropriate and safe way after three years (e.g., and files will be securely deleted from computers).

The file connecting subjects' names with their unique identification number will be kept in a password-protected file by the CC and on the GPI's computer for a minimum of three years, in accordance with IRB regulations, before being securely erased.

## **15.6 Protocol Deviations**

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

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

## **16 Publication policy**

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

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## **APPENDICES**

Appendix A: Schedule of Events

Appendix B: Baseline Data Collection

Appendix C: Follow-up data collection at time of cracked tooth treatment

Appendix D. Annual follow-up data collection

Appendix E. Subject retention plan

Appendix F. Patient Informed Consent Form

Appendix G. Quality Management Plan

Appendix H. Data Management Plan

Appendix I. Practitioner Informed Consent Sample



**APPENDIX A: Schedule of Events**

Procedures	Screening (Day -X to -Y)	Study Enrollment (Day 0)	Study 1 Year Visit (Day 365 -30 to +150)	Study 2 Year Visit (Day 730 -30 to +150)	Study 3 Year Visit (Day 1095 -30 until 10/31/2018)	Study Treatment Visit	Study Completion Visit (Day 1460 -30until 10/31/2018)	Premature
Informed Consent	X	X						
Assessment of Eligibility Criteria	X	X						
Review of Medical/Dental History	X	X						
Obtain or confirm contact information and preferred method of contact	X	X	X	X	X	X		
Oral Examination	X	X	X	X	X	X	X	X
External Cracked Tooth Assessment	X	X	X	X	X	X	X	X
Radiographs or Other Imaging*	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X )
Vitality Testing	X	X	X	X	X	X	X	X
Internal Crack Assessment						X		

\* Radiographs or other imaging will be undertaken if deemed necessary by the provider for the patient's dental care, not because of study participation.

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## Appendix B: Enrollment Data Collection

**Tooth #:** \_\_\_\_\_

**Patient demographics** (can be filled out before or after the clinical exam):

Age \_\_\_\_\_

Gender: M/F

Race:

Hispanic/Latino ethnicity: Y/N

Insurance status:

Highest education level attained: elementary/high school/college/graduate

**Patient-reported symptoms**

Spontaneous pain: Y/N

**Dentist assessment (Vitality must be confirmed with cold test, preferably using refrigerant spray)**

Biting pain: Y/N

Cold pain: Y/N

Cold pain lasts longer than 5 seconds: Y/N

**Study tooth characteristics (Assessment to include determination if each crack is tactilely perceptible with an explorer, and blocks transilluminated light)**

# of cracks: \_\_\_\_\_ Wear facet through enamel: Y/N Roots exposed to oral cavity: Y/N

Caries present: Y/N RPD abutment tooth: Y/N FPD abutment tooth: Y/N Non-carious cervical lesion present: Y/N Partial tooth fracture: Y/N Complete tooth fracture: Y/N

**Crack #1:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N

Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #2:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #3:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #4:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #5:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #6:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #7:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #8:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N  
Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects  
with restoration: Y/N Intersects with other crack(s): Y/N

**Restoration #1:** Location: M/D/O/F/L Material: amalgam/composite/cast  
metal/porcelain/PFM/RMGI/GI/Other:\_\_\_\_\_ Restoration clinically acceptable: Y/N

**Restoration #2:** Location: M/D/O/F/L Material: amalgam/composite/cast  
metal/porcelain/PFM/RMGI/GI/Other:\_\_\_\_\_ Restoration clinically acceptable: Y/N

**Restoration #3:** Location: M/D/O/F/L Material: amalgam/composite/cast  
metal/porcelain/PFM/RMGI/GI/Other:\_\_\_\_\_ Restoration clinically acceptable: Y/N

**Opposing tooth characteristics:**

Natural or restored tooth: Y/N Implant restored crown: Y/N Fixed Partial Denture (bridge)  
pontic: Y/N

Removable Full Denture or Partial Denture: Y/N No opposing tooth: Y/N

**Radiographic assessment** (optional)

Radiograph of cracked tooth within past year available: Y/N Evidence of crack: Y/N  
Periradicular lucency: Y/N

**Treatment recommended:**

Restoration: Y/N, If Y: Type: direct/indirect/intracoronal/crown/partial crown/build-up Bonded:  
Y/N

Endodontics: Y/N Extraction: Y/N

No treatment recommended \_\_\_\_\_

**Reason for recommended treatment:**

Caries (associated with crack): Y/N Caries (NOT associated with crack): Y/N

Broken/defective restoration: Y/N Compromised tooth structure (protection against tooth  
fracture): Y/N Periodontal involvement: Y/N Pulpal involvement: Y/N

Tooth sensitive to hot/cold: Y/N Tooth painful or infected: Y/N Broken tooth: Y/N

Other: \_\_\_\_\_

**Internal crack assessment after tooth preparation:**

# cracks assessed internally: \_\_\_\_\_

**Crack #1:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack includes:  
enamel/dentin Intersects with other crack(s): Y/N Crack involves: F  
cusps/Lcusps/Unsure/None Connected with pre-existing restoration: Y/N

**Crack #2:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack includes:  
enamel/dentin Intersects with other crack(s): Y/N Crack involves: F  
cusps/Lcusps/Unsure/None Connected with pre-existing restoration: Y/N

**Crack #3:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack includes:  
enamel/dentin Intersects with other crack(s): Y/N Crack involves: F  
cusps/Lcusps/Unsure/None Connected with pre-existing restoration: Y/N

**Crack #4:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack includes: enamel/dentin Intersects with other crack(s): Y/N Crack involves: F cusps/Lcusps/Unsure/None Connected with pre-existing restoration: Y/N

**Tooth treatment at this visit:**

Extraction: Y/N Endodontics: Y/N  
Restoration: Y/N, if Y: Location: M/D/O/F/L Type: direct/indirect/intracoronal/crown/partial crown/build-up Bonded: Y/N Material: amalgam/composite/cast metal/porcelain/PFM/RMGI/GI/Other: \_\_\_\_\_ Cement: Y/N, if Y: Type: GI/RMGI/resin/Other: \_\_\_\_\_

**Treatment recommended:**

Restorations Y/N, if Y: Type: direct/indirect/intracoronal/crown/partial crown/build-up Bonded: Y/N  
Endodontics: Y/N Extraction: Y/N Other: \_\_\_\_\_  
No treatment recommended \_\_\_\_\_

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## Appendix C. Follow-up data collection at time of cracked tooth treatment

Tooth #: \_\_\_\_\_

### **Patient-reported symptoms**

Spontaneous pain: Y/N

### **Dentist assessment (Vitality must be confirmed with cold test, preferably using refrigerant spray)**

Vital: Y/N/Unable to confirm Biting pain: Y/N Cold pain: Y/N Cold pain lasts longer than 5 seconds: Y/N

### **Study tooth characteristics**

(Assessment to include determination if each crack is tactilely perceptible with an explorer, and blocks transilluminated light)

# of cracks: \_\_\_\_\_ Wear facet through enamel: Y/N Roots exposed to oral cavity: Y/N

Caries present: Y/N RPD abutment tooth: Y/N FPD abutment tooth: Y/N Non-caries cervical lesion present: Y/N Partial tooth fracture: Y/N Complete tooth fracture: Y/N

**Crack #1:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N

Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #2:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #3:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #4:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #5:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #6:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #7:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #8:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

### **Opposing tooth characteristics:**

Natural or restored tooth: Y/N Implant restored crown: Y/N Fixed Partial Denture (bridge)  
pontic: Y/N  
Removable Full Denture or Partial Denture: Y/N No opposing tooth: Y/N

**Radiographic assessment** (optional)

Radiograph of cracked tooth within past year available: Y/N Evidence of crack: Y/N  
Periradicular lucency: Y/N

**Internal crack assessment after tooth preparation:**

# cracks assessed internally: \_\_\_\_\_

**Crack #1:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack includes:  
enamel/dentin Intersects with other crack(s): Y/N Crack involves: F  
cusps/Lcusps/Unsure/None Connected with pre-existing restoration: Y/N

**Crack #2:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack  
includes: enamel/dentin Intersects with other crack(s): Y/N Crack involves: F  
cusps/Lcusps/Unsure/None Connected with pre-existing restoration: Y/N

**Crack #3:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack  
includes: enamel/dentin Intersects with other crack(s): Y/N Crack involves: F  
cusps/Lcusps/Unsure/None Connected with pre-existing restoration: Y/N

**Crack #4:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack  
includes: enamel/dentin Intersects with other crack(s): Y/N Crack involves: F  
cusps/Lcusps/Unsure/None Connected with pre-existing restoration: Y/N

**Tooth treatment at this visit:**

Extraction: Y/N Endodontics: Y/N  
Restoration: Y/N, if Y: Location: M/D/O/F/L Type: direct/indirect/intracoronary/crown/partial  
crown/build-up Bonded: Y/N Material: amalgam/composite/cast  
metal/porcelain/PFM/RMGI/GI/Other: \_\_\_\_\_

**Treatment recommended:**

Restoration: Y/N, if Y: Type: direct/indirect/intracoronary/crown/partial crown/build-up Bonded:  
Y/N  
Endodontics: Y/N Extraction: Y/N  
No treatment recommended \_\_\_\_\_ Other: \_\_\_\_\_

**Reason for recommended treatment:**

Caries (associated with crack): Y/N Caries (NOT associated with crack): Y/N  
Broken/defective restoration: Y/N Compromised tooth structure (protection against tooth  
fracture): Y/N Periodontal involvement: Y/N Pulpal involvement: Y/N  
Tooth sensitive to hot/cold: Y/N Tooth painful or infected: Y/N Broken tooth: Y/N  
Other: \_\_\_\_\_

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## Appendix D. Annual Recall data collection

Tooth #: \_\_\_\_\_

### **Patient-reported symptoms**

Spontaneous Pain: Y/N

### **Dentist assessment (Vitality must be confirmed with cold test, preferably using refrigerant spray)**

Vital: Y/N/Unable to confirm Biting pain: Y/N Cold pain: Y/N Cold pain lasts longer than 5 seconds: Y/N

### **Study tooth characteristics**

#### **(Assessment to include determination if each crack is tactilely perceptible with an explorer, and blocks transilluminated light)**

# of cracks: \_\_\_\_\_ Wear facet through enamel: Y/N Roots exposed to oral cavity: Y/N

Caries present: Y/N RPD abutment tooth: Y/N FPD abutment tooth: Y/N Non-cariou cervical lesion present: Y/N Partial tooth fracture: Y/N Complete tooth fracture: Y/N

**Crack #1:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #2:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #3:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #4:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #5:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #6:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #7:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Crack #8:** Location: M/D/O/F/L Extends onto root: Y/N/Unsure Detectable with explorer: Y/N Blocks transilluminated light: Y/N Direction: vertical, horizontal, oblique Stained: Y/N Connects with restoration: Y/N Intersects with other crack(s): Y/N

**Restoration #1:** Location: M/D/O/F/L Material: amalgam/composite/cast  
metal/porcelain/PFM/RMGI/GI/Other: \_\_\_\_\_ Restoration clinically acceptable: Y/N  
**Restoration #2:** Location: M/D/O/F/L Material: amalgam/composite/cast  
metal/porcelain/PFM/RMGI/GI/Other: \_\_\_\_\_ Restoration clinically acceptable: Y/N  
**Restoration #3:** Location: M/D/O/F/L Material: amalgam/composite/cast  
metal/porcelain/PFM/RMGI/GI/Other: \_\_\_\_\_ Restoration clinically acceptable: Y/N

**Opposing tooth characteristics:**

Natural or restored tooth: Y/N Implant restored crown: Y/N Fixed Partial Denture (bridge)  
pontic: Y/N  
Removable Full Denture or Partial Denture: Y/N No opposing tooth: Y/N

**Radiographic assessment** (optional)

Radiograph of cracked tooth within past year available: Y/N Evidence of crack: Y/N  
Periradicular lucency: Y/N

**Treatment recommended:**

Restoration: Y/N, If Y: Type: direct/indirect/intracoronary/crown/partial crown/build-up Bonded:  
Y/N  
Endodontics: Y/N Extraction: Y/N  
No treatment recommended \_\_\_\_\_

**Reason for recommended treatment:**

Caries (associated with crack): Y/N Caries (NOT associated with crack): Y/N  
Broken/defective restoration: Y/N Compromised tooth structure (protection against tooth  
fracture): Y/N Periodontal involvement: Y/N Pulpal involvement: Y/N  
Tooth sensitive to hot/cold: Y/N Tooth painful or infected: Y/N Broken tooth: Y/N  
Other: \_\_\_\_\_

**Internal crack assessment after tooth preparation:**

**Crack #1:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack includes:  
enamel/dentin Intersects with other crack(s): Y/N Crack involves: F  
**Crack #2:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack includes:  
enamel/dentin Intersects with other crack(s): Y/N Crack involves: F  
**Crack #3:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack includes:  
enamel/dentin Intersects with other crack(s): Y/N Crack involves: F  
**Crack #4:** Location: M/D/O/F/L continuation of external crack: Y/N Stained: Y/N Crack includes:  
enamel/dentin Intersects with other crack(s): Y/N Crack involves: F

**Tooth treatment at this visit:**

Extraction: Y/N Endodontics: Y/N  
Restoration: Y/N, if Y: Location: M/D/O/F/L Type: direct/indirect/intracoronary/crown/partial  
crown/build-up Bonded: Y/N Material: amalgam/composite/cast



metal/porcelain/PFM/RMGI/GI/Other:\_\_\_\_\_ Cement: Y/N, if Y: Type:  
GI/RMGI/resin/Other:\_\_\_\_\_

**Treatment recommended:**

Restorations: Y/N, if Y: Type: direct/indirect/intracoronal/crown/partial crown/build-up Bonded:  
Y/N

Endodontics: Y/N Extraction: Y/N Other:\_\_\_\_\_

No treatment recommended \_\_\_\_\_

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## Appendix E. Subject retention plan

This Subject Retention Plan provides an outline of the issues associated with subject retention and the procedures for maximizing retention during the course of the Cracked Tooth Registry. For registries that involve longitudinal follow-up of study subjects, retention is a key requirement. High retention rates increase the validity and generalizability of registry data by ensuring that bias due to incomplete follow-up of subjects does not affect study findings.

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

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

**Missing Data:** Subjects still within the practice but follow-up visit is missed or data are not collected during visit.

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

**Unable:** Subjects 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 subject enrollment, emphasize study requirements to subjects:
  - a. They are part of a long-term (4 year) follow-up study, and the importance of annual assessments.
  - b. RCs or the CC will contact them by telephone to arrange follow-up visits even if they change dentists.
  - c. Entry criteria will include the ability and likelihood of maintaining participation throughout the study.
  - d. Collect information on:
    - i. Home address
    - ii. Home telephone number
    - iii. Cell phone number
    - iv. E-mail address(es)
    - v. Contact information (including cellular telephone and email) of two persons who do not live in the same household as the subject and who will know of the subject's whereabouts.
- 2) During study visits, confirm contact information (of subject and the two contact persons).
- 3) Have only one recall per year rather than two. Cracks in teeth progress relatively slowly and so yearly evaluation will suffice. For those teeth that get worse in the interim and require treatment, data will be collected at the treatment visits. Make contact with

participating offices and subjects every six months to remind them of upcoming recall intervals. The subject's preferred method of contact (e.g., postal mail, email, telephone) will be ascertained at the baseline appointment. Experience has shown that it is personal relationships, both between the subjects and offices, and the offices and the RCs, that promote successful execution of PBRN studies. In other words, it will be more meaningful for subjects to hear from their personal dental offices regarding a reminder for a study recall appointment. In turn, it will be more meaningful for the office to hear from its RC that it is time for them to contact subjects. It seems reasonable that the interim six-month contact be used to set up the specific recall appointment, which requires that the office be the entity to contact the subject. Experience has also shown that it is beneficial for the network to relieve burden on the practices. To that end, the National Dental PBRN will request IRB approval for the RCs and for the CC to receive the subject contact information and the contact information of two persons who do not live in the same household as the subject, so that both can assist the practices with follow-up contacts (e.g., birthday cards, recall visit reminders, etc), particularly with subjects who have had difficulty attending visits. The regions will have some latitude in determining the best means for maintaining contact with study subjects and ensuring their ongoing participation.

- 4) Number of Subjects per Practitioner Considerations:
  - a. Ask practitioners to enroll at least 10 and no more than 20 subjects, preferably during an 8 week enrollment period. Recruiting in a limited time period will make it easier to recall and follow the patients. Previous work found that 'cracks' are common such that enrolling 10 in a six week period should be feasible for virtually all practitioners.
- 5) Given the above design features, subjects should not be "lost". However, if a subject moves and contact is lost, the CC has extensive experience with using tracing resources such as National Change of Address services, motor vehicle departments, and LexisNexis databases. In those cases, the CC will implement those tracking procedures.
- 6) The process for contacting patients for recall visits and reminders will be for the practice to make the initial contact attempts, then inform their RC if there was no response within three weeks of the first contact attempt. The RC will then inform the CC, and the CC will initiate tracking procedures to identify updated patient contact information. Initiating tracking procedures promptly when there is no patient response to contact attempts will minimize missed study visits and also minimize loss to follow-up.

#### Methods to Minimize "Missing Data"

- 1) Put all participating practitioners on the same study schedule. Have an enrollment phase, then a break, then another specific follow-up phase of a couple of weeks and continue this cycle over the course of the study. Offices in general do a good job enrolling subjects because they are focused on the study every day during the enrollment period. However, it is more challenging to remember to perform study procedures when the enrollment phase is over and they may only have a study patient in the office once every couple of weeks. The patient has come and gone before they remember to do the study follow-up, even with the reminders that were put in place. So, over an 8 week period the office enrolls eligible subjects, with a goal of 10, but the flexibility to enroll up to 20 subjects within the enrollment period. Then over the next 10

months the intensity is much less, periodic check-in calls by RCs to ascertain staff turnover, data collection for internal crack characterization on teeth requiring treatment, etc. At one year it ramps up again and patients are seen specifically for a brief study visit.

- 2) Ask participating offices to develop a system to flag records of patients in their practices who are participating as subjects 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 subject is at the office, and can ensure that data collection takes place if indicated. Flagging the patient in the schedule will help to ensure that patients are not inadvertently scheduled when the practitioner will not be in the office. In the same way, if a subject's record is requested by another office, study personnel can inform the RC and attempts made to maintain the subject in the study.
- 3) Streamline follow-up data collection, so it won't be an involved recall exam.
- 4) Ask the practitioners to set aside specific time for follow-up assessments, perhaps 10 minutes, so they aren't trying to squeeze the recalls in with all their routine hygiene checks. With fewer subjects per practitioner, it seems like this might be more feasible.
- 5) Emphasize to practitioners as part of their initial study packages that the dentist has to be the motivational director of the study, especially regarding follow-up appointments, 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 in the 1<sup>st</sup> point above under “Lost” will also help reduce the number of subjects who refuse to continue participating. At enrollment, subjects are informed that they are agreeing/consenting to participate in a long-term follow-up study. Subjects who enroll are required to state a willingness to participate throughout the study.
- 2) The method described in the 3<sup>rd</sup> point above under “Lost” (making contact between visits) should also help reduce refusals. The CC has found that retention is increased if subjects are kept engaged and interested in the study through the use of periodic newsletters and other study updates, postcards, birthday cards, phone calls, using the patient's preferred mode of contact. Additionally, follow-up involvement will be kept as light and convenient for the subject as possible.

#### Methods to Minimize “Unable”

- 1) There are several scenarios in which a subject stops seeing the original/enrolling practitioner:
  - a. Subject does not move, but:
    - i. Subject changes dentists- in same practice
    - ii. Subject changes dentists- in different practice
    - iii. Subject stops seeing any dentist
  - b. Subject moves

- i. Subject sees new dentist
    - ii. Subject stops seeing any dentist
  - c. Dentist retires or dies
  - d. Dentist moves
  - e. Dentist refuses to continue participating (shouldn't happen)
- 2) The operational impact of all of the above scenarios can be summarized by two scenarios:
  - a. Subject has a new dentist (not a National Dental PBRN member)
  - b. Subject stops seeing any dentist
- 3) Locating the subject should not be a problem (see Methods to Minimize "Lost"), and having the subject agree to continue participating should not be a problem (see Methods to Minimize "Refused").
- 4) The main operational issue is: How to get study follow-up visit information from subjects seeing a non-National Dental PBRN dentist or not seeing any dentist.
  - a. Actively recruit the new dentist into the Network so the subject can continue to be followed by the new dentist.
  - b. Send the subject who is not seeing any dentist, or who is seeing a non-Network dentist who refuses to become a Network dentist, to a Network dentist in the area just for study follow-up visits (and have study pay for the visit).
  - c. Request permission from the new office and the patient to complete a chart abstraction to obtain data.

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

- 1) IRB/Informed Consent Considerations to Reduce Attrition
  - a. Incorporate into the informed consent form permission for all relevant study personnel, both in the dentist's office as well as the study investigators, and RCs to contact the subject. This will allow communications with the subject by study personnel without having to go through the dental office.
  - b. Incorporate into the informed consent form permission to see a National Dental PBRN provider other than the initial provider for the purpose of data collection. This will expedite data collection in those instances where a National Dental PBRN dentist retires or sells his/her practice, or where a subject goes to a different non-National Dental PBRN provider, or stops seeing a dentist for routine care.
- 2) Financial, but non-coercive incentive to patients to encourage continuing participation.

#### Additional Methods for Subjects who Have Missed a Recall Visit

- 1) If an enrolled patient misses the recall window for a visit, his or her contact information will be confirmed through the CC tracking procedures prior to the practice initiating contact attempts for the recall visit scheduling and the recall reminder for the next recall visit.

- 2) The practitioner's office will use the confirmed contact information to attempt to contact the patient by telephone (or other preferred means of contact) to schedule the next recall visit in a timely fashion, or remind the patient of the recall visit.
- 3) 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 visits.
- 4) If the patient cannot be reached, the two individuals designated as additional connections 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.
- 5) If their designees cannot be contacted, CC tracing resources will be used in an attempt to locate the patient to schedule the visit, or remind them of the visit.

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## Appendix F: Informed Consent Form

### Verbal Informed Consent Patient Information Sheet:



#### **Cracked Tooth Registry Study (National Dental PBRN)** **IRB Protocol Number: pending**

You are being asked to participate in the Cracked Tooth Registry Study. This study is being done by the National Dental Practice-Based Research Network, also called the National Dental PBRN. The National Dental PBRN is a network of dental practices committed to advancing knowledge by conducting research in their practices. Your dentist is participating in the National Dental PBRN and the Cracked Tooth Registry Study.

The purpose of this study is to determine the characteristics of cracked teeth and their treatment. You will not receive dental care as a study procedure, but will continue to receive dental care from your dentist as you would normally. If your dentist provides any treatment for your cracked tooth in the normal course of care, this treatment will be recorded separately for the study and followed for four years. By participating, you may help benefit patients in the future.

If you agree to be in this study, we will ask you to:

1. Allow us to evaluate and follow one permanent natural tooth in the back of your mouth.
2. Remain in the study for four years. You will be asked to return once each year for four years, because this is an important part of the study.
3. Allow us to contact you every six months or as needed. We may ask you questions about your tooth, as well as update your contact information. If you are not able to return to your dental office for your annual visit, we may ask you questions by telephone. We would ask information about any treatment that you had on the cracked tooth since your previous visit, such as whether or not the cracked tooth was removed. Therefore, please keep this tooth in mind and what happens to it, if anything, after you begin the study. You may be contacted by your dental office, the research network's regional coordinator staff, or the central data center in Maryland (called "Westat").
4. Provide us with names and contact information for two individuals who can be contacted by your dental office, the research network's regional coordinator staff, or the central data center in Maryland (called "Westat") for tracing and retention purposes only. We will not release any of your information to the two individuals, beyond informing them that we are trying to contact you on behalf of the dental office.

5. Allow us to record characteristics about yourself, such as age, race, ethnicity, sex, education, and dental insurance status.
6. Allow us to record information about your cracked tooth, the number of teeth that you have, and any symptoms from your tooth, such as pain. Information will be recorded at your first visit, when you have any treatment done on that tooth, and during your annual follow-up visits, for four years.
7. Allow us to contact your new dentist, if you change dentists during the course of the study. The new dentist will only be contacted to ask if they would be interested in participating in the study and continue to collect information about your cracked tooth until the conclusion of the study.

The research only involves collecting information. The information will be entered on forms at the time of your treatment and at certain times as described above. A risk of this study may be a breach of confidentiality.

You will receive a \$25.00 debit card at the enrollment visit and for each of the four annual study visits. This is a maximum of five debit cards for the total study, for a maximum of \$125.00. If you are discontinued from the study because your cracked tooth is removed, you will not receive any additional debit cards after the tooth is removed. There is no cost to you for participating in the study.

This research will not directly benefit you. Results of this study will help us understand how to improve dental care. This study may help dentists improve care for patients in the future. Significant new findings that develop during the course of the research may relate to your willingness to continue your participation in this study. If this occurs, these new findings will be provided to you.

The dental treatment that you receive today will not be affected by whether or not you choose to participate in this study. You can still have your cracked tooth treatment, if needed, but you do not have to have information collected. You are free to withdraw from this study at any time. You do not have to participate in this study. You are not waiving any of your legal rights by participating.

It is the intention of the network to publish quarterly newsletter regarding activities and study progress, including this study that you are participating in. If you would like to receive these quarterly updates, you may provide your dentist with your email address. The newsletters will be sent to you only by email.

Authorized persons from the University of Alabama at Birmingham and the Institutional Review Board have the right to review your research records and will protect the confidentiality of those records to the extent permitted by law. The study sponsor (National Institutes of Health) also has the right to review your research records to ensure that we have followed proper procedures. Otherwise, your research records will not be released without your consent unless required by law or a court order. If the results of this research are published or presented at scientific meetings, your identity will not be revealed.

If you have any questions about this research, please discuss them with your dentist. You may also call the director of the study at University of Alabama at Birmingham (UAB), Dr. Gregg Gilbert, at (205) 934-5423.

If you have any questions about your rights as a research participant, or concerns or complaints about the research, you may contact the Institutional Review Board for Human Use (OIRB) at the University of Alabama at Birmingham (UAB) at (205) 934-3789 or toll-free number at 1-855-860-3789. Regular hours



for the Office of the IRB are 8:00 a.m. to 5:00 p.m. Central Time, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

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## Appendix G: Quality Management Plan

This Study Quality Management Plan organizes the plans for QA/QC across the Cracked Tooth Registry Protocol Study Timeline and Study Activities. Some of the planned QA/QC is described in the main text of the protocol. Specifically, the QA/QC for Data Collection and Management is described in Section 9 above. The Subject Retention Plan in Appendix E is also a key component of QA/QC of subject recall visits. The Data Management Plan described in Appendix H below will contain the specific plan for Quality Management of Data Collection and Management. The step by step data QA/QC process at the Regional Administrative Site is included in Section 9.7 of the Cracked Tooth Registry study MOP. A Roadmap for data management QA/QC and Monitoring RC tasks is also provided in Appendix T of the MOP.

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

1. **Practitioner Recruitment, Training, and Enrollment:**
  - a. The RCs who will be recruiting practitioners within each region will work with the practitioners to assure that they understand the expectations of them for the study and assure the quality of practitioner recruitment and enrollment.
  - b. The Study Manager will ensure the proper enrollment of practitioners and their locations' study personnel into the IRB system. Through this activity, the Study Manager will also provide QA/QC of the recruitment across regions according to the protocol and procedures, and will help troubleshoot recruitment/enrollment issues.
2. **Subject screening and enrollment:**
  - a. Proper training of the practitioners and study personnel at the practitioners' locations by the RC on the protocol and procedures as outlined in the study Manual of Procedures (MOP) is a planned QA activity. This will assure that the practitioners are ready to conduct the subject screening and enrollment in accordance with the protocol.
  - b. The RC will be a resource for the practitioners and study personnel to ask questions during subject screening and enrollment. The Study Manager will keep a log of problems encountered and solutions across regions and RCs. This will assure consistency of solutions to problems encountered by practices across RCs and Regions. The RC will also use the log to create a regularly updated 'Frequently Asked Questions' document that will be available to all practices, so that they have a resource for finding information and solutions for commonly encountered problems.
  - c. As the practitioners and each practice are anticipated to be busy dental practices, the study is designed to provide the practitioners with extensive support of the RC, the Study Manager, and the CC. Where possible, QA/QC will be assisted by or performed by the RC, the Study Manager, or the CC to allow the practitioner efforts to be focused on subject enrollment and follow-up. Each practice will maintain a Consented Patient Log and will send a copy to the RC regularly, during Enrollment for Intensive Data Review.

**3. Subject Follow-up:**

- a. The QA/QC activity described under 2b above will be continued until all subject follow-up is complete.
- b. Further QA/QC of subject follow-up is described in the Subject Retention Plan in Appendix E.

**4. Data Collection:**

- a. After the patient's visit, the practitioner will perform a QC check to confirm the data on the CRFs. The practitioner will then sign form to attest to the accuracy and completeness of that CRF. CRFs that are completed by the patient will be reviewed by the practitioner or practice staff upon completion to ensure that all questions were answered.
- b. The Primary RC will perform a QC check of the paper CRFs. For the first patient for each practitioner and then 20-25% of patients thereafter, the Primary RC will perform Intensive Data Review. Once the data is entered in the database by the primary RC, another RC will complete QA review of data entered.
- c. Further details regarding QA/QC of data collection are contained in Section 9 and Appendix H and Section 9 of the Cracked Tooth registry study MOP.

**5. Data Analysis and interpretation:**

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

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

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

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## Appendix H: Data Management Plan

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

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## Appendix I: Practitioner Informed Consent Form

### Consent Form To Participate In Research For National Dental PBRN Practitioners

**TITLE OF RESEARCH:** Cracked Tooth Registry Study (National Dental PBRN)  
**IRB PROTOCOL:** Pending  
**INVESTIGATOR:** Dr. Gregg H. Gilbert at the University of Alabama at Birmingham  
**SPONSOR:** National Institutes of Health

#### Explanation of Procedures

You are being asked to participate in a research study being conducted by the National Dental Practice-Based Research Network (National Dental PBRN). The purpose of the Cracked Tooth Registry Study is to assess characteristics of initially symptomatic and asymptomatic cracked teeth and follow these teeth to record changes that occur over time. You are eligible to participate because you:

- (1) completed a National Dental PBRN enrollment questionnaire that described your dental practice;
- (2) completed Financial Conflict of Interest training;
- (3) attended a National Dental PBRN orientation session or watched a video or PowerPoint presentation that discussed key principles in participating in National Dental PBRN research projects;
- (4) completed certification in human participants research;
- (5) signed the Individual Investigator Agreement and completed a W-9 form;
- (6) discussed with your National Dental PBRN Regional Coordinator the proper procedures for doing studies with human participants and reviewed procedures specific to this Cracked Tooth Registry Study;
- (7) are willing to recruit 10-20 eligible subjects within the enrollment period, who expect to remain in the practice for the four-year study duration, and who express willingness to return for follow-up visits;
- (8) are willing to appoint enrolled subjects annually for follow-up over 4 years to assess progression and treatment of cracked teeth;
- (9) are willing to allow your dental practice, Regional Coordinator, and Coordinating Center (Westat) to contact subjects as needed for recall visits, recall reminders, or information about their cracked teeth;
- (10) are willing to work with Regional Coordinators to clarify any data issues.

Information from your enrollment questionnaire and other National Dental PBRN studies in which you participate will be linked using your assigned practitioner ID number. This will allow us to see how characteristics from each of these studies might be related to each other.

All findings will be reported anonymously and in the aggregate, using statistical summaries. If you like, we can compare your results to all the others who participated in this study and report that back to you. This would be done anonymously with no identification of other dentists participating in these studies.

To participate in the Cracked Tooth Registry Study, we will want you to discuss the progress of the study and the accuracy of data collection forms with your Regional Coordinator after you begin enrolling patients, as well as on an as-needed basis by telephone or in-office visits to document your compliance with IRB regulations and the data recording protocol. The National Dental PBRN Regional Coordinator assigned to your practice is:

Name: \_\_\_\_\_

E-mail: \_\_\_\_\_

Telephone: \_\_\_\_\_

### Risks and Discomforts

The Cracked Tooth Registry Study only involves recording information about patients and routine treatment in your practice. A risk of this study may be a breach of confidentiality.

### Benefits

This research may or may not directly benefit you. Results of this study will help us understand dental care and how to improve dental care.

### Significant New Findings

Significant new findings that develop during the course of the research that may relate to your willingness to continue your participation in this study will be provided to you.

### Alternatives

The dental treatment that you provide will not be affected by whether or not you choose to participate. You do not have to participate in this study.

### Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of National Institutes of Health; the U.S. Food and Drug Administration (FDA); and the Office for Human Research Protections (OHRP). The results of the research may be published for scientific purposes. However, your identity will not be revealed.

If you leave your practice, we will attempt to follow the enrolled patients who remain at your current practice location. If enrolled patients leave your practice, we will attempt to contact them during the study period to obtain information about their cracked teeth.

### Refusal or Withdrawal without Penalty

You are free to withdraw your consent and discontinue participation at any time without penalty against further care or research at the University of Alabama at Birmingham.

### Cost of Participation

There will be no cost to you for participating.

### Payment for Participation in Research

The Cracked Tooth Registry Study involves collecting information on patient eligibility and diagnosis prior to treatment, explaining the studies to the patient and obtaining informed consent, and collecting information regarding the cracked tooth following treatment. You will be compensated for the time required to do the research, receiving \$50 for each baseline visit completed, \$25 for each follow-up visit completed, and \$25 for the first treatment visit for each patient. This first treatment can be provided at the baseline exam, annual visit, or out of sequence visit. Practitioners will be paid for only one (first) treatment visit per patient during the entire study period. Payment will be made via a single check after each data collection phase. This check will be mailed to you within 60 days after you have returned all forms to your Regional Coordinator and their legibility and accuracy have been verified.

You should keep a copy of the Cracked Tooth Registry Study Data Collection Forms so that you can refer to them at later visits if needed, and send the original Data Collection Form to your Regional Coordinator.

### Questions

If you have any questions, concerns, or complaints about the research, including available treatments, please contact Dr. Gregg Gilbert. He will be glad to answer any of your questions. Dr. Gilbert's number is 205-934-5423.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the Institutional Review Board for Human Use (OIRB) at the University of Alabama at Birmingham (UAB) at 205-934-3789 or toll-free number at 1-855-860-3789. Regular hours for the Office of the IRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else

### Legal Rights

You are not waiving any of your legal rights by signing this consent form.

### Signatures

Your signature below indicates that you agree to participate in this study. You will receive a copy of this signed document.

\_\_\_\_\_  
Signature of Practitioner

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Witness

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Principal Investigator Reviewing Consent Document

\_\_\_\_\_  
Date



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**University of Alabama at Birmingham**  
**AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION**  
**FOR RESEARCH**

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**What is the purpose of this form?** You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant name: \_\_\_\_\_ UAB IRB Protocol Number: Pending  
Research Protocol: Cracked Tooth Registry Study Principal Investigator: Dr. Gregg Gilbert  
(National Dental PBRN) Sponsor: National Institutes of Health

**What health information do the researchers want to use?** All dental information and personal identifiers of whatever kind related to or collected for use in the research protocol.

**Why do the researchers want my health information?** The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

**Who will disclose, use and/or receive my health information?** Any of the following may disclose, use and/or receive your health information: the investigators and staff working on the research protocol (whether at UAB or elsewhere) as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies.

**How will my health information be protected once it is given to others?** Your health information will be given to UAB personnel associated with the study. All information is stored in a secure manner. It is possible that the study sponsor (the National Institutes of Health) would also request this information. If we forward the information to the study sponsor or if we are required by court order to provide any information to an entity that is not required to follow federal privacy laws, we cannot assure that the information will remain protected.

**How long will this Authorization last?** Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

**Can I cancel the Authorization?** You may cancel this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

**Can I see my health information?** You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: \_\_\_\_\_ Date: \_\_\_\_\_  
or participants' legally authorized representative: \_\_\_\_\_ Date: \_\_\_\_\_

Printed Name of participant's representative: \_\_\_\_\_

Relationship to the participant: \_\_\_\_\_