PERI-OPERATIVE TOOTH PAIN

NIXDORF STUDY 17

A. INTRODUCTION, GOALS and SPECIFIC AIMS

Brief overview: Pain following root canal therapy occurs commonly, with publications suggesting an incidence range of 3% to 58% (Sathorn, Parashos, & Messer, 2008) depending on the definition. The majority of this post-endodontic pain is well controlled using current treatment modalities (Hargreaves, Keiser, & Byrne, 2006), but a small subset of patients seems to be resistant to treatment and experience severe pain (Shabahang et al., 2005). Significant post-endodontic pain is commonly referred to as an endodontic flare-up and has been defined as severe pain that precipitates a patient-dentist interaction within one week of treatment initiation. Such pain, when associated with local soft tissue swelling, is known to occur in 3% of all cases of root canal therapy (Walton & Fouad, 1992). Given that there are over 16.4 million root canal therapies performed every year within the United States (American Dental Association, 2002), about half a million patients experience severe pain that is resistant to treatment every year. This pain is known to cause significant amounts of dental anxiety and fear (Logan et al, 2001), which in turn is a major barrier to receiving dental care (Eitner et al., 2006; Hagglin et al., 2000; Sohn & Ismail, 2005; Woolfolk et al., 1999) and can have other negative psychosocial consequences (Locker, 2003). For these reasons, it is important to understand the factors related to the development of endodontic flare-up pain in efforts to better treat this pain.

Research on endodontic-related pain has suggested that (a) the intensity of pre-operative pain and (b) the experience of intra-operative pain are significant factors related to the subsequent development of persistent tooth pain (i.e., pain present 6+ months following root canal therapy) (Polycarpou et al., 2005). Unfortunately, little research exists that relates these pain experiences and other clinical variables with the development of post-root canal flare-up pain. Furthermore, the relationship between post-root canal flare-up pain and persistent tooth pain at 6 months is unknown. Therefore, the **primary goal of this study** is to assess the presence and magnitude of pre-operative and intra-operative tooth pain, and to determine how these factors are associated with the outcome of intense post-endodontic flare-up pain. The overall goal is to better understand how the experience of peri-operative pains relate to each other.

The **long-term goal** of this line of research is to identify the modifiable pre-operative factors that put patients at greater risk of developing persistent tooth pain following root canal therapy, thereby providing evidence that will allow dentists to act preventively to mitigate this risk, improve pain control, increase their patients' quality of life, and decrease the number of dental emergency interactions. Since future studies within the DPBRN will be required to achieve this long-term goal, the **secondary goal of this study** is to assess the feasibility of recruiting patients using the DPBRN and to pilot test a more detailed data collection procedure from both patients and practitioners using a small subset of practitioners and within the DPBRN. As an initial step towards the long-term goals, the following specific aims are proposed for this peri-operative pain study:

Aim 1: Document, by survey, *the relationship of the patient's pre-operative, intra-operative, and post-operative pain associated with receiving initial orthograde root canal therapy on an adult tooth.*

1.1 Assess the presence and intensity of **pre-operative tooth pain**, as measured by the Graded Chronic Pain Scale (GCPS).

1.2 Evaluate the occurrence and intensity of **intra-operative tooth pain** immediately following the procedure, as measured by a component of the Graded Chronic Pain Scale (GCPS).

1.3 Evaluate the occurrence and intensity of **post-operative tooth pain**, during the first week, as measured by the Graded Chronic Pain Scale (GCPS).

1.4 Test for the presence of statistically significant associations between the primary outcome of short-term post-operative pain and each of the following: (a) pre-operative pain and (b) intra-operative pain.

Aim 2: Assess the feasibility *of using the DPBRN to enroll 48 dentists who are to recruit 600 patients receiving root canal therapy; and pilot test a more comprehensive data collection regimen with a subset of dentists within the Minnesota region only.*

2.1 Estimate the number of root canal treated patients that can be recruited per month by dentists within the DPBRN.

2.2 Estimate the proportion of returned and useable patient and practitioner questionnaires collected by the DPBRN.

2.3 Determine the additional time required to complete the more comprehensive data collection protocol (to be completed by 40 patients, 4 dentists, and the Minnesota regional coordinator).

2.4 Determine the percentage of pre-operative and post-operative periapical radiographs that are of diagnostic quality, as determined by an endodontist and an oral and maxillofacial radiologist. (Radiographs are to be obtained for the 40 patients and the 4 dentists engaged in the more comprehensive data collection protocol.)

B. BACKGROUND and SIGNIFICANCE

B. 1. Occurrence and burden of post-endodontic flare-up pain

Significant tooth pain occurring within one week following root canal therapy, referred to as post-endodontic flare-up pain, has been reported to occur for 1.6% to 6.6% of root canal procedures (Al-Negrish & Habahbeh, 2006; Eleazer & Eleazer, 1998; Imura & Zuolo, 1995; Morse et al., 1987a; Morse et al., 1987b; Trope, 1991; Walton & Fouad, 1992; Yoldas et al., 2004). This pain, which has been well described within the literature, is specifically defined as severe pain (≥7 on an 11-point numerical rating scale of 0-10) occurring in or around the location of a tooth that received root canal therapy within the last week. Pain experienced during and after root canal therapy is known to cause significant amounts of dental anxiety and fear (Logan et al., 2001), which in itself is a major barrier to receiving dental care (Armfield, Stewart, & Spencer, 2007; Eitner et al., 2006; Hagglin et al., 2000; Sohn & Ismail, 2005; Woolfolk et al., 1999) and has other negative psychosocial consequences (Locker, 2003). Post-endodontic flare-up pain is also associated with lost productivity for both the patient and the dentist, because of the frequent need for emergent appointments for re-evaluation (Walton & Fouad, 1992). Together, these issues are significant, because 16.4 million root canal therapies are performed every year within the United States (American Dental Association, 2002). This suggests that **half a million patients experience post-endodontic flare-up pain each year**.

B. 2. Current treatment approaches for post-endodontic flare-up pain

Post-endodontic flare-up pain is typically treated with various short-term prescription analgesic regimes, taken orally when the pain becomes severe, with co-administration of antibiotics. This treatment approach is very effective for the majority of patients (Hargreaves, Keiser, & Bryne, 2006), **but current management approaches do not address the analgesic needs of the approximately 3% of patients experiencing flare-up pain** (Shabahang et al., 2005).

B. 3. Factors associated with the development of post-endodontic flare-up pain

One possible reason for the lack of analgesic efficacy is that once severe pain occurs, there are plastic changes in the innate pain modulation system (Baron, 2006; Dionne, Kim, & Gordon, 2006; Treede et al., 2000; Woolf & Salter, 2000) that are long-lasting (Juhl et al., 2006) and reduce the analgesic efficacy of medications (Kissin, 2000). **Pre-surgically administrating medications known to inhibit the plastic**

changes that occur within the pain modulation system, known as pre-emptive analgesia, has shown some promise in being able to reduce post-surgical pain (Ho, Gan, & Habib, 2006; Nikolajsen et al., 2006; Wilson et al, 2008). These results suggest that this is a modifiable pathway related to decreasing post-surgical pain (Gottschalk & Smith, 2001). Application of this approach to treatment is being touted for use with dental procedures (Fletcher & Spera, 2002). The research proposed in this application is needed to unequivocally establish the relationships between peri-operative tooth pain, so that future research focusing on improving pain outcomes will have known estimates to assess the therapeutic response of pain interventions.

B. 4. Summary and direction of future research

To reduce the occurrence of post-endodontic flare-up pain, dentists need to rapidly assess the factors that put their patients at risk for it. Dentists also need to be able to identify those risk factors that are modifiable. Research has elucidated a number of risk factors associated with the development of post-endodontic flare-up pain, but most are not modifiable. In non-dental surgeries, pre-existing pain has been related to the development of severe short-term post-operative pain (Macrae & Oakley Davies, 1999). Therefore, **a more complete understanding of the factors related to the development of peri-operative pain will allow for development of more effective strategies to reduce the occurrence of post-endodontic flare-up pain**.

C. PRELIMINARY STUDIES

Section B referred to data from previous studies regarding pain associated with root canal therapy. Pilot studies on this topic have not been performed within the DPBRN, but prior experience by other investigators within the DPBRN has shown all of the following:

- Private practitioners in this network can be engaged in research and readily participate in research projects;
- Practitioner and patient recruitment has exceeded initial goals and does not limit completion of research protocols;
- Regional coordinators can implement all aspects of research protocols (*e.g.*, obtaining IRB approval and maintaining communication with practitioner-investigators);
- The coordinating center provides adequate oversight of the regional sites and management of the network as a whole;
- Protocol working groups can prepare research protocols, provide topical expertise when needed, and create drafts of manuscripts; and
- Executive and administrative bodies can provide appropriate support and direction to allow research concepts to be developed and ultimately result in publication.

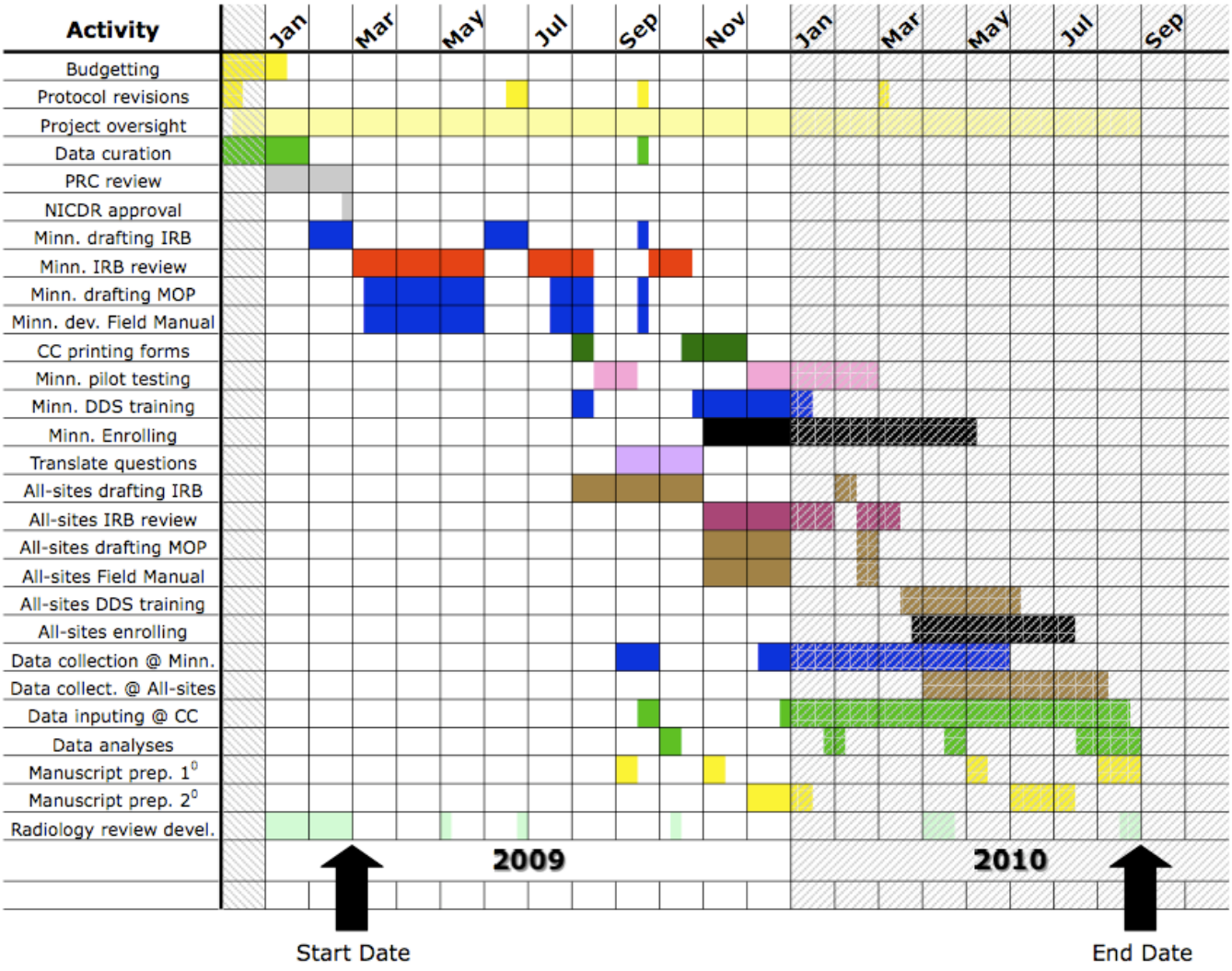
D. RESEARCH DESIGN and METHODS

D.1. Study design and overview

This endodontic study has cross-sectional and longitudinal components. The study will involve the participation of 48 practitioner-investigator dentists from the Dental Practice-Based Research Network (DPBRN) who will recruit patients -- 600 over the course of 6 months -- receiving initial root canal therapy. The DPBRN is a group of dental practices that have been linked together to investigate research questions and to share experiences and expertise. A comprehensive description of the DPBRN is provided in the parent U01 grant application, which has been provided to the DPBRN Protocol Review Committee. An additional resource is the DPBRN's web site at http://www.DentalPBRN.org.

There are two major advantages to using the DPBRN to investigate epidemiological aspects of root canal therapy. The first advantage is the ability to recruit from a large, diverse population of dentists and patients. This will allow rapid accrual of cases with a small burden on individual practitioner-investigators and regional coordinators. The second advantage is that the diverse geographic and ethnic representation in this large private practice research network allows for greater generalizability of the results to the population of interest, that being people receiving root canal therapy within the United States of America. The areas represented in the United States include approximately 50 dentists in each of the Portland, Oregon and Minneapolis-St. Paul metropolitan areas, over 200 dentists in Florida and Georgia, over 800 in Alabama and Mississippi, and approximately 40 in Scandinavia.

Timeline for this study



D.2. Eligibility criteria

Patients will be informed about the study and initially screened for eligibility by their dentist before initiation of root canal therapy. Patients who are interested in participating will document their informed consent as described in section E. Practitioners will confirm the patient's eligibility by completing a brief clinical exam

form. This "Initial Evaluation" form (see **Appendix 2**) has been pilot tested and takes approximately 2 minutes to complete. Inclusion and exclusion criteria for patient enrollment are as follows:

Inclusion criteria

- 19-70 years old
  This is the age range for the majority of people who present for root canal therapy on permanent teeth.
- Permanent adult tooth requiring its first non-surgical root canal therapy
  Patients with more than 1 tooth requiring root canal therapy are eligible, but only the first root canal procedure performed will be included to avoid problems of correlation within patients.

Exclusion criteria

- Evidence of prior root canal therapy, including iatrogenic but not disease-induced pulp access, of the tooth being considered.
  Inclusion of previously treated teeth will make it unclear whether resultant persistent pain is associated with this prior treatment or attempt at treatment.

- Patient with obvious cognitive impairments (*e.g.*, past stroke with communication deficits, dementia, mental disability).
  Patients will need to be able to provide a reasonably accurate pain history.
- Patient unable to return for follow-up in 6 months, since another study plans to obtain data on these patients at that time.

D.3. Target enrollments

The target enrollment is 12 endodontists and 36 general practitioners, with representation from all 5 regional sites. The Minnesota region will field test the data collection process before implementation within the other regions. Because IRB approval for the Minnesota region will have already been obtained, this site will likely recruit a greater number of dentists and patients, up to 50% of the totals. We anticipate a 3:1 ratio of generalists to endodontists. This equates to enrolling 6 endodontists and 18 general dentists from the Minnesota region and 1-2 endodontists and 4-5 general dentists from the other four regions. Patient recruitment will occur over 6 months. This requires **each generalist to recruit 1-2 patients per month** and **each specialist to recruit 4-5 patients per month**. Since the secondary goal of this study is to assess patient enrollment for a future research proposal, there are no specific enrollment restrictions by practitioner type (generalist vs. specialist), tooth (anterior vs. posterior), numbers of patients per practitioner, or number of patients per region.

D.4. Outcome measures

All data will be obtained by use of questionnaires. The outcome measure of pre-operative, intra-operative and post-operative pain will be assessed using the Graded Chronic Pain Scale (GCPS). The GCPS is a reliable and valid pain measurement tool that has been used extensively in epidemiological studies (Von Korff et al., 1992; Smith et al., 1997; Von Korff, 2001). Pre-operative pain intensity is defined in this instrument by, "*In the past one week, on average, how intense was your tooth pain rated on a 0 to 10 scale?*"

Several potential risk factors, obtained from questionnaires answered by patients and dentists, will be assessed for correlations with the outcome of short-term post-operative pain. These variables can be grouped into the following categories:

- Patient characteristics (*i.e.,* age, gender, tooth, pulp status, presence of periapical periodontitis) (Torabinejad et al., 1988; Trope, 1991; Walton & Fouad, 1992);
- Pain measures (*i.e.*, pre-operative pain intensity, intra-operative pain) (Imura & Zuolo, 1995);
- Psychosocial variables (*i.e.*, dental anxiety, dental fear) (Neverlien, 1990; Neverlien & Backer Johnsen, 1991);
- Medical characteristics (*i.e.*, smoking, diabetes) (Fouad & Burleson, 2003; Krall et al., 2006; Marending, Peters, & Zehnder, 2005);
- Procedural characteristics (*i.e.*, type of root canal, number of appointments, use of rubber dam, procedural difficulty) (Torabinejad et al., 1988; Trope, 1991; Walton & Fouad, 1992).

When available, questions used successfully in previous epidemiological research (e.g., Women's Health Initiative; see Margolis et al., 2008) were included in questionnaires. When such questions were not available, questions were used that were empirically found to be useful and routinely used in clinical practice, both academic (University of Minnesota) and private (Dental Specialists practice).

D.5. Discussion of protocol with practitioner-investigators

Before data collection begins, DPBRN Project Coordinating staff will have a face-to-face meeting with participating practitioner-investigators and their staff. This meeting provides an opportunity for DPBRN staff to explain the protocol and address any questions that dentists and their staff might have. Study procedures, including human subjects/informed consent issues, will be reviewed. The Data Collection Forms will be explained, including the definitions and criteria for data to be entered and the terms used. Instructions for proper completion of the Data Collection Forms will be reviewed. Printed instructions for filling out the forms will also be provided.

D.6. Data collection process and estimated time burden

Stickers

Per Nixdorf email dated 7/6/2009: All forms will be printed at UAB. Also, Joshua is in favor and I agreed to printing 3 sets of forms for each patient, with **stickers** for anything over 3 appointments. Yes, most may not be used, but the CC would like additional copies in the hands of the patients/dentists to cover things like a torn/messed up/misplaced form and to decrease errors with stickers.

Bar-coded forms

We will use the bar-coded forms generated at the CC at UAB. We at HP will conduct some very limited on-going data collection (2-3 items) to permit midterm analysis. Completed surveys will be mailed to UAB for final data entry and analysis. Data from the web surveys will be sent electronically according to the parameters set forth by the CC's statisticians and programming staff.

Consecutive log
Age Range
Hispanic/non-Hispanic

Per Nixdorf conference call 7/14/09: due to concerns about collecting PHI on patients who do not consent to be in study, on the consecutive log, we will collect an age range. Furthermore, we would like to collect if patient is Hispanic or non-Hispanic.

Form 4 Pre-operative patient questionnaire: Prior to root canal therapy and before the administration of local anesthetics, patients need to complete the first 5 questions of an 18-item baseline questionnaire (see **Appendix 1**; 3 minutes to complete). The remaining questions are completed after the

application of local anesthetic, but before initiation of root canal therapy. Completed questionnaires will be given to staff within the dental practice to be submitted with the dentist's questionnaires.

Form 9 Intra-operative patient questionnaire: Within the first hour after each root canal therapy appointment, patients will complete a 5-item intra-operative questionnaire (see **Appendix 1**; less than 1 minute to complete). Patients will mail this questionnaire directly to the regional coordinating center, using the self-addressed pre-paid postage envelope. This is done to reduce biases in patient responses, since dental office staff will not see these data. Of special note: when root canal treatment is provided over two or more appointments, the patient will need to complete a separate questionnaire following each appointment.

1-Hour Post Treatment - Misnomer

Per Nixdorf email dated 7/6/2009: The '1-hour' term is a bit of a misnomer. The time actually refers to the time following the appointment in which the form needs to be completed. So, 1 second after the appointment is better than 1 minute > 30 minutes > 1 hour. So yes, they can start immediately following the appointment. But we need to be careful about the DDS and staff influencing the reporting of the data...

Post-operative patient questionnaire: One week following each root canal therapy appointment, the patient will complete an 11-item post-operative questionnaire (see **Appendix 1**; 2 minutes to complete). This questionnaire, along with its self-addressed pre-paid postage envelope, will be given to the patient prior to leaving the dental office following each root canal procedure. A reminder telephone call, or e-mail if that is the patient's preferred method of communication, will be sent by the regional coordinating center to the patient on the day before the questionnaire needs to be completed. If this questionnaire is not received by the regional coordinating center within 3 business days following the due date, a second reminder message will be sent to the patient that includes the questionnaire. One week past the due date, a third and final reminder message will be sent to the patient by the regional coordinating center. Of special note: when root canal treatment is provided over two or more appointments, the patient will need to submit a separate questionnaire following each appointment.

Pre-operative dentist questionnaire*:* Before treatment, the dentist will complete a 15-item questionnaire that covers the topics of patient eligibility, consent, and diagnosis (see **Appendix 2**; 2 minutes to complete). The 9 clinical questions involve information that is routinely gathered during normal clinical practice and therefore do not require deviation from standard practice (Berman & Hartwell, 2006). The dentist can likely provide the responses to these 9 questions after the initiation of care, such as administration of local anesthetic, since this information is gathered when establishing and documenting the diagnosis for the treated tooth.

Post-operative dentist questionnaire: After treatment, a 10-item questionnaire needs to be completed (see **Appendix 2**; 1 minute to complete). Of special note: when root canal treatment is provided over two or more appointments, the dentist will need to complete a separate questionnaire following each appointment.

Comprehensive version of data collection protocol

A more comprehensive set of patient questionnaires, which will assess psychosocial variables such as depression and anxiety (see **Appendix 3**), will be pilot tested with 40 patients enrolled by 4 practitioner-investigators. These 4 dentists will not only complete the pre- and post-operative questionnaires described above, but also submit pre-operative and post-oburation periapical radiographs. Radiographs will be interpreted by two independent and blinded dentists following standardized criteria. This more comprehensive data collection protocol is being tested only in the Minnesota region to reduce the burden on the regional coordinating centers. The 4 practitioner-investigators will be chosen to represent the various practice types present in the DPBRN (*i.e.*, general versus specialty practice, private versus corporate business structure.

Attention will be paid to ensure that practices using both film and digital radiographs will participate in this pilot project, so that handling of both forms of imaging can be tested. Data regarding time to complete these questionnaires, as well as the dentists' overall satisfaction with the data collection process, will be obtained and used to assess feasibility of this expanded protocol.

D.7. Data management and quality assurance procedures

Individual practitioner-investigators and patients will record data on paper forms. Forms will be mailed to the regional coordinating center to be scanned into electronic images, then sent to the coordinating center. Professional data entry staff at the coordinating center will use a dual monitor system to view the electronic image on one monitor and enter data into a second. The data will be organized into identifiable batches for data entry, with two samples of 10% of the forms to be selected re-entry. The first batch of data will be re-entered by the original data entry technician to determine intra-rater reliability and the second by a different technician for inter-rater reliability. If the discrepancy rate for either re-entry sample is above 0.5%, then the full batch will be re-entered. Re-training may be necessary if unacceptable error rates continue to occur.

All electronic data will be stored on a secure network drive with restricted access. All personnel at the Coordinating Center are required to have current IRB and HIPAA training certification, and all must sign confidentiality forms. All paper copies will be stored in a secured room. The data will be stored using the current version of ACCESS or SQL database software packages. The database programming staff will work with the Coordinating Center investigators and Network Chair to make sure that the required systems are available on time and function efficiently. Members of the Coordinating Center statistical consulting unit will prepare the final dataset and documentation. Data analyses will be performed by one member of the statistical consulting unit and subsequently verified by another, using the SAS® statistical software system.

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

A DPBRN regional coordinator will be assigned responsibility for each practitioner-investigator and their practice. Telephone contact will be initiated with practitioner-investigators and their practice during the first week of their participation in the study. Subsequent contact will occur during week 2 and on a monthly basis thereafter. The regional centers will assess the progress of each practitioner-investigator to that date and answer any questions they may have. This monitoring will also involve asking practitioners or their staff to fax or email to the DPBRN regional coordinator, or staff assigned to the practice, a small number of initially completed forms. This will allow the DPBRN regional coordinator, or staff member, to review the forms for completeness and legibility. Immediately following this review and any necessary discussion with the practitioner-investigator, these faxed or emailed forms will be destroyed. Face-to-face meetings will be held with the practitioner-investigator and their practice staff at the discretion of the regional center assigned to the practice.

D.9. Statistical analysis

This study has two aims, each with several specific sub-aims. The first aim is to recruit 600 patients undergoing root canal therapy to investigate the occurrence and intensity of three types of dental pain: 1) pre-operative, 2) intra-operative, and 3) short-term post-operative. At all 3 times, pain will be measured using the GCPS (0-10 scale). Pre- and intra-operative pain will be dichotomized as any pain outcome (*i.e.*, GCPS ≥1 vs. GCPS 0). Post-operative pain will be dichotomized as severe pain (*i.e.*, GCPS ≥7 vs. <7), because severe intensity of pain is required to meet the definition of post-endodontic flare-up pain.

The analyses for specific sub-aims 1.1, 1.2, and 1.3 will be to present summaries of the outcome measures. For the scores from the GCPS, summaries will include means and standard deviations as well as medians,

inter-quartile ranges, and histograms. The overall proportion of patients with post-operative pain will be reported with 95% confidence intervals and also computed using logistic regression and generalized estimating equations (GEE) to account for nesting. The analyses for specific aim 1.4 will explore the relationship of pre- and intra-operative pain with the main outcome, post-endondontic flare-up pain. The first approach will be to use logistic regression with GEE to model the relationship between the pre-operative pain rating and the dichotomous outcome of flare-up pain. This will then be repeated using intra-operative pain as the primary independent variable. The next step will be to model the presence of post-operative flare-up pain as a function of both pre- and intra-operative pain and their interaction, as well as patient-level factors. Of particular interest is whether the measurements of pre- and intra-operative pain contribute independently to the final model. The above analyses will then be repeated explicitly examining the effect of modifying variables, such as practitioner type (general dentist vs. endodontist), including practitioner type as a covariate in multivariate models. There are likely important clinical reasons influencing the outcomes of root canal therapy, such as reasons for referral to an endodontist, so that data must be interpreted with care.

The second aim is to assess feasibility of the recruitment goals under the first group of aims, to assess the quantity and quality of data collected, and to pilot test a more comprehensive data collection regimen. The first two items (sub-aims 2.1 and 2.2) are to estimate the number of patients recruited per month and the proportion of patient questionnaires completed and returned. These estimates will be calculated and reported with 95% confidence intervals. Furthermore, they will be calculated both overall and separately for practitioner type (general dentist vs. endodontist). The next item (sub-aim 2.3) will rely on self-reports from 4 Minnesota dentists and the Minnesota regional coordinator to quantify how much time is required to complete the more comprehensive data protocol as piloted on 40 patients. These results will be presented as a mean with standard deviation and as a histogram. The last item (sub-aim 2.4) will quantify the proportion of periapical radiographs considered to be of diagnostic quality among the same pilot-testing cohort of 40 patients and 4 practitioners. The proportion will be reported with a 95% confidence interval. In addition, the two independent raters will compile a list of reasons for insufficient radiograph quality.

D.10. Sample size and power considerations

The number of patients was selected based on the study's primary goal of determining the occurrence of short-term post-operative pain following root canal therapy, with consideration given to the need for 6-month follow-up planned for the DPBRN persistent tooth pain study (see separate protocol for details). The calculations do not explicitly address the possibility of clustering within practitioners, largely because we expect the vast majority of variability to be at the patient level and because there are no available data from which to estimate intraclass correlations (ICC). The standard procedure is to adjust the sample size by a factor $D=[1+\rho(m-1)]$, where m is the number of subjects within each cluster and ρ is the ICC. In this case there is the potential for two types of clustering—within endodontists and within general dentists. If we conservatively assume an ICC of 0.05 within endodontists and 0.025 among general dentists, with a total of 300 subjects for each group of dentists, the factors are 2.20 and 1.28 for the two groups respectively. We assume a higher ICC among endodontists because of the possibility that their patient populations will be more homogeneous with respect to their dental problems and outcomes. This leads to an effective sample size of 136 for the endodontic patients and 255 for the generalist patients for an overall effective sample size of 391. This is comfortably within our targeted minimal sample size of 300 to measure an overall proportion. Determining the number of subjects required to estimate the proportion experiencing short-term post-operative pain is straightforward, but it depends both on the proportion of subjects who develop persistent pain as well as the desired precision. Previously reported research suggests that from 1% to 5% (proportions of 0.01 to 0.05) of people undergoing successful root canal therapy subsequently develop short-term post-operative pain. For example, estimating the proportion 1% with precision of +/-1% requires 381 subjects while estimating a proportion of 5% with the same precision of +/-1% requires 1825 subjects. Fortunately, as the observed proportion increases, the precision can be less stringent. For instance, estimating a proportion of 5% with a precision of +/-3% (range of 2 to 8%) is likely to be tolerable while estimating a proportion of 2% with precision of +/-3% is inadequate as

the range includes the nonsensical value of -1%. The table below, generated by nQuery Advisor 6.01 software, shows the required number of patients (**n**) to estimate the proportion with 95% confidence for a reasonable range of observed proportions and precisions. For high proportions it is no longer necessary for the estimate to be so precise. Columns 4 through 7 illustrate how reducing the precision impacts the required sample size: when the proportion is 3% a precision of +/-2% requires only 280 subjects while a proportion of 5% with a precision of +/-3% requires 457 subjects. It seems reasonable to base the sample size on an expected proportion of 3%, thus requiring about 300 patients to measure the observed proportion with <2% precision for each practice type (generalist versus specialist), or 600 patients total.

Sample sizes (n) estimating proportions within a given precision at 95% confidence.

	a	b	c	d	e	f	g
Expected proportion (%)	1%	3%	3%	3%	5%	5%	5%
Precision (+/- %)	1%	1%	2%	3%	1%	2%	3%
Estimated sample size, n	381	1118	**280**	125	1825	457	203

E. HUMAN SUBJECT RESEARCH

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

Human subjects' involvement and characteristics: This protocol involves human subjects. The human subjects directly involved in this study are the patients who have sought dental treatment in the practitioner-investigator's practices. The practitioner-investigators will be recruited from the clinicians enrolled in DPBRN and meet the eligibility criteria specific to this protocol. Participating in the data collection and returning Data Collection Forms will constitute consent by the practitioner-investigators.

Sources of materials: Data will be obtained from the Data Collection Forms that each practitioner-investigator completes and radiographic images that they take, both in digital and film format. Data will also be obtained from patients as a result of their completing pain and quality of life questionnaires.

Potential risks: The only risk to the practitioner-investigators and their patients will be the unlikely accidental disclosure of health care provider and patients' health information. However, every precaution will be taken to prevent such disclosures. No experimental techniques or materials will be used and the burden on the patients, clinicians and dental office staff, will be the same as that experienced as part of regular dental treatment, except that an Informed Consent Form and Data Collection Forms given to each patient to complete in the study. The treatment sessions will, therefore, will be slightly longer in order to record on these forms the necessary requested information. The Data Collection Forms will be coded, kept confidential, and will be stored in a secure place.

E.2. Adequacy of protection against risk

Recruitment and informed consent: We will provide the practitioner-investigators and their patients' information that explains the nature of the study, time commitment involved, any risks involved, and compensation information. We will also answer any questions they may have in a telephone conversation or in face-to-face discussion with them. A specially designed Informed Consent Form will be explained to the patient by the practitioner-investigators. After assurance that the information provided is understood by the patient the patient and practitioner-investigator both sign the form, which then becomes part of the patient's chart or is stored in a secure research folder.

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

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

Practitioner-investigators will benefit from the opportunity to reflect their views on root canal therapy treatment and gain information on the practice methods of their peers. The indirect benefit to the patients may be the ultimate improvements in dental treatment regularly provided in daily clinical practice. The potential benefits to the practitioners, and indirectly to their patients, will exceed the risk involved with the participation. The practitioner-investigators will charge their normal fees for the treatment provided.

Subjects will not be paid for their participation in completing the pre-operative or intra-operative questionnaires, but will be remunerated a total of $10 when the final post-operative questionnaire is received by the regional coordinating center. DPBRN practitioner-investigators will be remunerated $50 per completed set of questionnaires returned to regional coordinating center and verified to be. Practitioner-investigators in the PDA and HP organizations will not receive payment directly. Instead, a single lump sum payment will be paid to their organizations and this payment will indirectly contribute to remuneration.

E.4. Importance of the knowledge to be gained

The knowledge to be gained from this study has the potential to change the daily practice of dentistry. It will make dentists within the DPBRN more aware of the magnitude of the problem of short-term pain following root canal therapy and identify the associated risk factors are related to why this pain occurs. If modifiable risk factors associated with the procedural delivery of care can be identified as anticipated, this research will support future research that will assess outcomes of clinical interventions addressing these modifiable risk factors.

E.5. Inclusion of women

Both genders will be eligible to enroll as patients within this study, as will they be eligible to participate as practitioner-investigators. We anticipate that approximately 55% of the patients enrolled will be female, which is similar to percentages seen in normal clinical practice.

E.6. Inclusion of minorities

Racial and ethnic minorities to be included in the study will likely be proportional to their composition in the communities that they draw from. The racial and ethnic distribution expected to participate in the study is shown in the first Targeted/Planned Enrollment table of this application.

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

The practitioner-investigators who participate in this study will be dental practitioners enrolled in the DPBRN and meet the other eligibility criteria. The patients will be given an explanation of what the study entails and

they will also sign an informed consent to participate. No gender or racial/ethnic group will be excluded. Our anticipated enrollment for patients is shown in the Targeted/Planned Enrollment table of this application.

E.8. Inclusion of children

Children, defined as 18 years and younger, are not to be included in this study since they have few permanent teeth, low treatment need for root canal therapy, have not undergone reliability testing for the primary outcome measure, and are rarely seen in the orofacial pain clinic for evaluation of persistent tooth pain. Patients 19 years old or older will be enrolled in the study. Because persons less than 21 years old comprise 'children' in the NIH definition, a small percentage of patients (probably about 2% of the enrollees) in the study will be children according to the NIH definition.

Targeted/Planned Enrollment Table (for the patients participating)

Study Title: **Peri-operative Tooth Pain**

Total Planned Enrollment: 600 patients

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	33	27	60
Not Hispanic or Latino	297	243	540
Ethnic Category: Total of All Subjects *	330	270	600
Racial Categories			
American Indian/Alaska Native	4	2	6
Asian	7	5	12
Native Hawaiian or Other Pacific Islander	3	3	6
Black or African American	53	43	96
White	263	217	480
Racial Categories: Total of All Subjects *	330	270	600

F. VERTABRATE ANIMALS

N/A

G. LITERATURE CITED

Al-Negrish, A. R., & Habahbeh, R. (2006). Flare up rate related to root canal treatment of asymptomatic pulpally necrotic central incisor teeth in patients attending a military hospital. *Journal of Dentistry, 34*(9), 635-640. doi:10.1016/j.jdent.2005.12.007

American Dental Association. (2002). *Survey of dental services rendered and distribution of dentists in the united states by region and state,1999*

Armfield, J. M., Stewart, J. F., & Spencer, A. J. (2007). The vicious cycle of dental fear: Exploring the interplay between oral health, service utilization and dental fear. *BMC Oral Health, 7*, 1. doi:10.1186/1472-6831-7-1

Baron, R. (2006). Mechanisms of disease: Neuropathic pain--a clinical perspective. *Nature, Clinical Practice Neurology, 2*(2), 95-106.

Berman, L. H., & Hartwell, G. R. (2006). Diagnosis. In S. Cohen, & K. M. Hargreaves (Eds.), *Pathways of the pulp* (Ninth ed., pp. 1-39). St. Louis: Mosby Elsevier.

Dionne, R. A., Kim, H., & Gordon, S. M. (2006). Acute and chronic dental and orofacial pain. In S. B. McMahon, & M. Koltzenburg (Eds.), *Wall and melzack's textbook of pain* (Fifth ed., pp. 819-835). London: Elsevier Churchill Livingstone.

Eitner, S., Wichmann, M., Paulsen, A., & Holst, S. (2006). Dental anxiety--an epidemiological study on its clinical correlation and effects on oral health. *Journal of Oral Rehabilitation, 33*(8), 588-593.

Eleazer, P. D., & Eleazer, K. R. (1998). Flare-up rate in pulpally necrotic molars in one-visit versus two-visit endodontic treatment. *Journal of Endodontics, 24*(9), 614-616.

Fletcher, M. C., & Spera, J. F. (2002). Pre-emptive and postoperative analgesia for dentoalveolar surgery. *Oral and Maxillofacial Surgery Clinics of North America, 14*(2), 137-151.

Fouad, A. F., & Burleson, J. (2003). The effect of diabetes mellitus on endodontic treatment outcome: Data from an electronic patient record. *Journal of the American Dental Association (1939), 134*(1), 43-51; quiz 117-8.

Gottschalk, A., & Smith, D. S. (2001). New concepts in acute pain therapy: Preemptive analgesia. *American Family Physician, 63*(10), 1979-1984.

Hagglin, C., Hakeberg, M., Ahlqwist, M., Sullivan, M., & Berggren, U. (2000). Factors associated with dental anxiety and attendance in middle-aged and elderly women. *Community Dentistry and Oral Epidemiology, 28*(6), 451-460.

Hargreaves, K. M., Keiser, K., & Byrne, B. E. (2006). Analgesics in endodontics. In S. Cohen, & K. M. Hargreaves (Eds.), *Pathways of the pulp* (Ninth ed., pp. 668-690). St. Louis: Mosby Elsevier.

Ho, K. Y., Gan, T. J., & Habib, A. S. (2006). Gabapentin and postoperative pain--a systematic review of randomized controlled trials. *Pain, 126*(1-3), 91-101.

Imura, N., & Zuolo, M. L. (1995). Factors associated with endodontic flare-ups: A prospective study. *International Endodontic Journal, 28*(5), 261-265.

Juhl, G. I., Svensson, P., Norholt, S. E., & Jensen, T. S. (2006). Long-lasting mechanical sensitization following third molar surgery. *Journal of Orofacial Pain, 20*(1), 59-73.

Kissin, I. (2000). Preemptive analgesia. *Anesthesiology, 93*(4), 1138-1143.

Krall, E. A., Abreu Sosa, C., Garcia, C., Nunn, M. E., Caplan, D. J., & Garcia, R. I. (2006). Cigarette smoking increases the risk of root canal treatment. *Journal of Dental Research, 85*(4), 313-317.

Locker, D. (2003). Psychosocial consequences of dental fear and anxiety. *Community Dentistry and Oral Epidemiology, 31*(2), 144-151.

Logan, H. L., Lutgendorf, S., Kirchner, H. L., Rivera, E. M., & Lubaroff, D. (2001). Pain and immunologic response to root canal treatment and subsequent health outcomes. *Psychosomatic Medicine, 63*(3), 453-462.

Macrae, W. A., & Davies, H. T. O. (1999). Chronic postsurgical pain. In I. K. Crombie, P. S. Croft, S. J. Linton, L. LeResche & M. Von Korff (Eds.), *Epidemiology of pain* (pp. 125-142). Seattle: IASP Press.

Marending, M., Peters, O. A., & Zehnder, M. (2005). Factors affecting the outcome of orthograde root canal therapy in a general dentistry hospital practice. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics, 99*(1), 119-124.

Margolis, K. L., Qi, L., Brzyski, R., Bonds, D. E., Howard, B. V., Kempainen, S., et al. (2008). Validity of diabetes self-reports in the women's health initiative: Comparison with medication inventories and fasting glucose measurements. *Clinical Trials, 5*, 240-247.

Morse, D. R., Furst, M. L., Belott, R. M., Lefkowitz, R. D., Spritzer, I. B., & Sideman, B. H. (1987a). Infectious flare-ups and serious sequelae following endodontic treatment: A prospective randomized trial on efficacy of antibiotic prophylaxis in cases of asymptomatic pulpal-periapical lesions. *Oral Surgery, Oral Medicine, and Oral Pathology, 64*(1), 96-109.

Morse, D. R., Furst, M. L., Belott, R. M., Lefkowitz, R. D., Spritzer, I. B., & Sideman, B. H. (1987b). A prospective randomized trial comparing periapical instrumentation to intracanal instrumentation in cases of asymptomatic pulpal-periapical lesions. *Oral Surgery, Oral Medicine, and Oral Pathology, 64*(6), 734-741.

Neverlien, P. O. (1990). Assessment of a single-item dental anxiety question. *Acta Odontologica Scandinavica, 48*(6), 365-369.

Neverlien, P. O., & Backer Johnsen, T. (1991). Optimism-pessimism dimension and dental anxiety in children aged 10-12 years. *Community Dentistry and Oral Epidemiology, 19*(6), 342-346.

Nikolajsen, L., Finnerup, N. B., Kramp, S., Vimtrup, A. S., Keller, J., & Jensen, T. S. (2006). A randomized study of the effects of gabapentin on postamputation pain. *Anesthesiology, 105*(5), 1008-1015.

Polycarpou, N., Ng, Y. L., Canavan, D., Moles, D. R., & Gulabivala, K. (2005). Prevalence of persistent pain after endodontic treatment and factors affecting its occurrence in cases with complete radiographic healing. *International Endodontic Journal, 38*(3), 169-178.

Sathorn, C., Parashos, P., & Messer, H. (2008). The prevalence of postoperative pain and flare-up in single- and multiple-visit endodontic treatment: A systematic review. *International Endodontic Journal, 41*(2), 91-99.

Shabahang, S., & American Association of Endodontics Research and Scientific Affairs Committee. (2005). State of the art and science of endodontics. *Journal of the American Dental Association, 136*(1), 41-52; quiz 89-90.

Smith, B. H., Penny, K. I., Purves, A. M., Munro, C., Wilson, B., Grimshaw, J., et al. (1997). The chronic pain grade questionnaire: Validation and reliability in postal research. *Pain, 71*(2), 141-147.

Sohn, W., & Ismail, A. I. (2005). Regular dental visits and dental anxiety in an adult dentate population. *Journal of the American Dental Association (1939), 136*(1), 58-66; quiz 90-1.

Torabinejad, M., Kettering, J. D., McGraw, J. C., Cummings, R. R., Dwyer, T. G., & Tobias, T. S. (1988). Factors associated with endodontic interappointment emergencies of teeth with necrotic pulps. *Journal of Endodontics, 14*(5), 261-266.

Treede, R. D., Apkarian, A. V., Bromm, B., Greenspan, J. D., & Lenz, F. A. (2000). Cortical representation of pain: Functional characterization of nociceptive areas near the lateral sulcus. *Pain, 87*(2), 113-119.

Trope, M. (1991). Flare-up rate of single-visit endodontics. *International Endodontic Journal, 24*(1), 24-26.

Vlaeyen, J. W., & Crombez, G. (2007). *Fear and pain*. Seattle, WA: IASP Press.

Von Korff, M. (2001). Epidemiologic and survey methods: Chronic pain assessment. In D. Turk, & R. Melzack (Eds.), *Handbook of pain assessment: Second edition* (Second ed., pp. 603-618). New York: Guilford Press.

Von Korff, M., Ormel, J., Keefe, F. J., & Dworkin, S. F. (1992). Grading the severity of chronic pain. *Pain, 50*(2), 133-149.

Walton, R., & Fouad, A. (1992). Endodontic interappointment flare-ups: A prospective study of incidence and related factors. *Journal of Endodontics, 18*(4), 172-177.

Wilson, J. A., Nimmo, A. F., Fleetwood-Walker, S. M., & Colvin, L. A. (2008). A randomised double blind trial of the effect of pre-emptive epidural ketamine on persistent pain after lower limb amputation. *Pain, 135*(1-2), 108-118.

Woolf, C. J., & Salter, M. W. (2000). Neuronal plasticity: Increasing the gain in pain. *Science, 288*(5472), 1765-1769.

Woolfolk, M. W., Lang, W. P., Borgnakke, W. S., Taylor, G. W., Ronis, D. L., & Nyquist, L. V. (1999). Determining dental checkup frequency. *Journal of the American Dental Association, 130*(5), 715-723.

Yoldas, O., Topuz, A., Isci, A. S., & Oztunc, H. (2004). Postoperative pain after endodontic retreatment: Single- versus two-visit treatment. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics, 98*(4), 483-487.