PERSISTENT TOOTH PAIN

Study 18

A. INTRODUCTION, GOALS and SPECIFIC AIMS 1
Overview: 1
Aim 1: Document, by survey 2
Aim 2: Assess the feasibility 2
B. BACKGROUND and SIGNIFICANCE 2
B.1. Definition and terminology used to describe persistent pain associated with root canal therapy 2
B.2. Epidemiologic research for persistent pain associated with root canal therapy 3
B.3. Potential impact of this research 4
C. PRELIMINARY STUDIES 5
D. RESEARCH DESIGN and METHODS 6
D.1. Overview 6
Study Timeline 7
D.2. Patient recruitment and feasibility 7
D.3. Outcome measures 7
D.4. Data collection. 8
Three months after initiation of root canal therapy 8
Six months after initiation of root canal therapy 8
Comprehensive version of data collection protocol 8
D.5. Data management and quality assurance procedures 9
D.6. Statistical analysis 9
D.8. Sample size and power considerations 10
E. HUMAN SUBJECT RESEARCH 10
E.1. Risks to the patients and health care providers 10
Human subjects' involvement and characteristics 10
Sources of materials 11
Potential risks 11
E.2. Adequacy of protection against risk 11
Recruitment and informed consent 11
Protection against risks 11
E.3. Potential benefits of the proposed research to the subjects and others 11
Remuneration 11
E.4. Importance of the knowledge to be gained 12
E.5. Inclusion of women 12
E.6. Inclusion of minorities 12
E.7. Information to be provided for all clinical research studies 12
E.8. Inclusion of children 12
Targeted/Planned Enrollment Table (for the patients participating) 13
F. VERTABRATE ANIMALS 13
G. LITERATURE CITED 13

A. INTRODUCTION, GOALS and SPECIFIC AIMS

Overview: Dentists perform over 16.4 million root canal therapies every year in the United States (American Dental Association, 2002). Persistent tooth pain, which is pain present 6 months after root canal therapy, is known to occur following root canal therapy in a fashion similar to other post-surgical pains, such as phantom limb pain (Marbach, 1978). Research in this area is limited, but suggests a frequency of occurrence of 3% to 12% for persistent post-root canal pain (Campbell, Parks, & Dodds, 1990; Marbach et al., 1982; Polycarpou et al., 2005) and 6% for all types of tooth pain (Moana Filho et al., 2008). Despite the commonality of root canal

treatment, the occurrence and severity of persistent tooth pain and extent of interference with daily life from this condition has not been well studied in dental care populations. Adequate treatments for some of these pains are emerging, and early identification and treatment may improve prognosis (Vanotti et al., 2007), but the first step is to determine how widespread the problem is and how severely it affects dental patients.

A precise estimate of the occurrence of persistent tooth pain following root canal therapy, as well as an evaluation of its effects and a determination of the risk factors involved, would be of great significance to patients and providers. This knowledge is expected to influence patient and provider decisions about dental treatment and to facilitate the development of preventative treatment strategies, such as pre-emptive analgesia, aimed at reducing patients' modifiable peri-operative risk factors. These issues have been identified as priorities by various groups, namely dentists performing root canal therapies (http://www.aae.org/foundation/grants_awards/fdnresearchgrant.htm), dentists involved in treating persistent tooth pain (Lavigne & Sessle, 2004), and patients who suffer with this type of pain (http://www.fpa-support.org/).

The **long-term goal** of this line of research **is to identify pre-operative factors** that put patients at greater risk for 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, and increase their patients' quality of life. For this long-term goal to be realized, future externally funded research using the DPBRN is anticipated; hence, there is a need for pilot data to support the feasibility of such research. As a step towards achieving this long-term goal, the following specific aims are proposed for this study:

Aim 1: Document, by survey, *the occurrence of tooth pain present 6 months after root canal therapy in the 600 patients recruited for the DPBRN peri-operative tooth pain study*.

1.1 Estimate the **frequency of occurrence and intensity** of persistent tooth pain, as measured by the Graded Chronic Pain Scale (GCPS).

1.2 Assess the **interference with daily life** of persistent tooth pain, as measured by the GCPS.

1.3 Identify a limited number of potential **risk factors**, such as intensity of pre-operative pain and occurrence of intra-operative tooth pain, for persistent tooth pain 6 months following root canal therapy.

Aim 2: Assess the feasibility *of obtaining 6-month follow-up data on the patients enrolled in the DPBRN 'peri-operative tooth pain' study and, using a subset of dentists only in the Minnesota region, pilot test a more comprehensive data collection protocol*.

2.1 Estimate the 6-month survey return rate of the 600 patients previously enrolled by the DPBRN and who were treated with root canal therapy.

2.2 Estimate the percentage of patients returning for the 6-month clinical evaluation from the previously enrolled 40 patients participating in the comprehensively assessment pilot within the Minnesota region.

2.3 Determine the additional time required to complete the more comprehensive data collection protocol performed by the subset of 40 patients and 4 dentists, as well as additional time of the Minnesota regional coordinating team.

2.4 Determine the percentage of 6-month follow-up periapical radiographs that are of diagnostic quality, as determined by 2 dentists, an Endodontist and Oral & Maxillofacial Radiologist, obtained from 40 patients by the 4 dentists using the more comprehensive data collection protocol

B. BACKGROUND and SIGNIFICANCE

B.1. Definition and terminology used to describe persistent pain associated with root canal therapy

Root canal therapy is a treatment routinely provided in dental offices throughout the United States and Scandinavia. Between 1990 and 1999, the number of root canals performed in the United States increased by 13% to nearly 16 million (www.aae.org/rootcanalspecialists/patients/factsheet.htm). Persistent pain after these

procedures has been investigated in four studies (summarized in B.2), giving rise to occurrence estimates of 3 to 12% of all cases (Campbell et al., 1990; Lobb, Zakariasen, & McGrath, 1996; Marbach et al., 1982; Polycarpou et al., 2005). To extrapolate this to a conservative estimate for the United States, since more than 16.4 million root canal therapies are performed each year, approximately 500,000 new cases of persistent pain are thought to occur associated with this common dental treatment.

Notably, it is unknown to what extent dental patients are burdened by this pain. There are reports that among patients who undergo general surgical operations, up to 30% develop persistent pain; moreover, of the patients who develop persistent pain, up to one third experience pain that is sufficiently burdensome to be considered disabling (Jensen & Nikolajsen, 1999; Kehlet, Jensen, & Woolf, 2006; Macrae & Davies, 1999). The burden of persistent pain has not been reported by any studies investigating dental procedures, such as root canal therapy or tooth extraction. If the same 3:1 ratio is present with root canal therapy as seen with other surgical procedures, then overall we would expect 3% of patients to report persistent pain and 1% of patients to report persistent pain with high levels of interference with daily life.

Persistent pain after nerve sectioning is not a newly recognized phenomenon in healthcare; historic reports refer to it as ‘phantom limb pain’ (Jensen & Nikolajsen, 1999). In 1978, the term ‘phantom tooth pain’ was coined to describe pains after amputation of dental pulps via root canal therapy (Marbach, 1978). Other terms have been used to describe similar tooth-related pain presentations, such as idiopathic periodontalgia (Harris, 1974), idiopathic odontalgia (Graff-Radford & Solberg, 1986), and atypical odontalgia (Rees & Harris, 1979). In this research protocol, the term ‘persistent pain’ is used because it is generic, descriptive in nature, eliminates confusion with previously used terminology that may be associated with specific pain mechanisms, and most notably, causation by the root canal therapy is not implied since often pre-existing pain is present.

B.2. Epidemiologic research for persistent pain associated with root canal therapy

Endodontic literature suggests that root canal therapy has a success rate of 80 to 98% (Friedman, Abitbol, & Lawrence, 2003; Friedman & Mor, 2004; Kojima et al., 2004). The definition of “success” varies among the studies and is often limited solely to radiographic findings (Basmadjian-Charles et al., 2002). While presence of pain following surgical and non-surgical root canal treatment has been assessed (Hoskinson et al., 2002; Rahbaran et al., 2001), few studies have focused on the persistence of pain in the presence of radiographic healing (Polycarpou et al., 2005).

Four studies have reported the occurrence of persistent pain associated with root canal therapy. The first study (Marbach et al., 1982) consisted of a mail survey to 732 patients who had received root canal treatment by one endodontist. It is unknown whether these patients presented for initial root canal therapy or for non-surgical re-treatment, or even surgical re-treatment. The mailed questionnaire consisted of 10 questions, which were not published, that retrospectively elicited information about the patient’s tooth and facial pain before and after root canal therapy based on patient recollection. The usable return rate was 63% (510) without mention of the measures employed to obtain a higher response rate. Of the patients who responded, 56% (256) were female. Phone follow-up was performed for the patients who answered positively to the question of “tooth pain for 1 month after endodontic therapy.” Of the 30 patients with pain, half consented to re-evaluation and were seen. Eleven patients were female, of whom 8 “presented evidence of phantom tooth pain.” The criteria for this diagnosis were not clarified. The results of the 4 male patients were not presented or discussed. The authors’ conclusion was “…between 3 and 6 percent [persistent pain associated with root canal therapy] is possible.” There was no direct mention of risk factors, but female gender may be a variable related to the development of persistent pain associated with root canal therapy in this study.

The second study (Campbell et al., 1990) used a questionnaire sent to 206 patients who initially had non-surgical root canal treatment followed by surgical treatment. The reasons why the patients had returned or the diagnosis requiring surgical intervention were not reported. Patients were mailed questionnaires consisting of 8 questions that were not published, which elicited information about the presence or absence of pain, type of pain, and whether the pain was continual. The usable return rate was 57% (118) without mention of the measures employed to obtain a higher response rate. Of the patients who responded, 57 (48%) were female

and the average age was 49 years old. The 6 (5%) positive respondents were evaluated, and no abnormalities were revealed either clinically or radiographically. On average, they had experienced post surgical pain for 21 months. The authors reported that three patients (2.5%) had pain prior to surgery that persisted unchanged, which led to the diagnosis of 'phantom tooth pain'. Three patients (2.5%) developed pain following surgery, leading to the diagnosis of 'post-traumatic dysesthesia'. Of the three patients with pain that persisted, pain had been present for 1, 4, and 36 months before non-surgical treatment had been initiated. Of the 6 teeth with persistent pain, 4 were maxillary teeth (1 molar, 1 premolar and 2 incisors) and 2 were mandibular (1 premolar, 1 canine). There was no direct mention of risk factors, but female gender, maxillary arch, and posterior tooth position may be related to development of persistent pain associated with root canal therapy in this study.

The third study (Lobb et al., 1996) consisted of telephone follow-up of 198 patients who were initially evaluated during a study assessing post-endodontic treatment pain over the first 3 post-operative days. A total of 83% (165) were contacted at 1 year and completed a follow-up questionnaire. Undefined post-operative pain was identified by 13% (21) of the patients as a problem with their root canal treatment at an undefined time. The authors noted that patients with problems did not seek care by revisiting the endodontist who originally treated the tooth. Despite the statement that, "The goal is to ascertain which factors may be significantly correlated within intra-operative and post-operative pain experience for predictive modeling purposes," the article presented no data that discussed variables associated with persistence of pain.

The fourth study (Polycarpou et al., 2005) prospectively enrolled 400 patients who received root canal therapy at a teaching hospital and consented to at least a 12-month follow-up examination. Data were collected on demographic variables, tooth type and location, type of endodontic care provided, pre-, intra- and post-operative pain history, dental history, clinical evaluation, and periapical radiographs. A total of 175 (44%) patients returned for follow up. Of the original patient population of 400, 224 (56%) did not have any follow-up data (30% could not be contacted, 15% subsequently had the tooth extracted with no follow-up data, 9% were non-compliant in returning, and 2% had died). A total of 21 teeth (12%) of 175 had radiographic signs of healing and persistent pain 12 months or more after root canal therapy. Using logistic regression for individual variables gave the following odds ratios (95% CI): presence of preoperative tooth pain for ≥3 months 8.60 (1.88-39.29); previous chronic pain problem 4.52 (1.51-13.52); inter-appointment pain 3.93 (1.44-10.69); pre-operative pain in tooth 7.80 (1.71-35.66); pre-operative tooth sensitivity to percussion 7.80 (1.71-35.66) history of painful treatment in the orofacial region 3.83 (1.35-10.90); female gender 4.47 (1.22-16.37); and surgical treatment 3.96 (1.08-14.57). Besides the large amount of dropouts, this study did not protect against enrolling patients who already had the outcome in question -- persistent tooth pain -- which would exist in a tertiary referral center's patient population. This is likely why large point-estimate odds ratios were observed for variables such as the presence of preoperative tooth pain for ≥3 months, inter-appointment pain, pre-operative pain in tooth, pre-operative tooth sensitivity to percussion, and history of painful treatment in orofacial region.

B.3. Potential impact of this research

The proposed research will elucidate the occurrence, magnitude, and interference with daily life from persistent pain following root canal therapy. Little research has been reported on this topic despite the startling high occurrence (30%) of persistent pains reported in association with other surgical procedures (Kehlet et al., 2006). If persistent pain associated with root canal therapy is common, for example 3% from the current literature, then approximately **500,000 new cases of persistent pain are occurring every year** in the United States (based on an estimated 16.4 million root canals per year, American Dental Association, 2002). The available research on this problem has significant limitations, and an occurrence rate as high as 3% is contrary to general clinical impression. Thus, the results of the proposed will fill an important and clinically relevant knowledge gap, with the potential to change the delivery of root canal therapy and have implications for dental surgery procedures in general.

Clinical experience has shown that the human cost of persistent pain can be high (Kehlet et al., 2006). Many patients with persistent pain associated with root canal therapy suffer significant levels of pain and are disabled, but reliable estimated are not known. Furthermore, these patients may seek care from multiple healthcare providers in desperate attempts to stop their persisting pain, incurring high medical bills and missed work days

(Allerbring & Haegerstam, 2004). Little information about the burden on the patient who is experiencing persistent tooth pain has been reported in the dental literature. It is our assumption that a subset of the patients experiencing persistent pain will develop interference with daily life associated with such pain. This subgroup is of greatest interest, since they are the most likely to repeatedly seek treatment and be the most difficult to treat (Allerbring & Haegerstam, 1993; Allerbring & Haegerstam, 1995; Allerbring & Haegerstam, 2004; Haegerstam & Allerbring, 1995).

Knowing the number, resultant burden, and risk factors would have **ramifications for dental treatment planning.** For example, with knowledge of the occurrence and subsequent risk for persistent pain, greater efforts to reduce dental pulp-related pathology and conserve tooth structure -- both time-honored concepts in dentistry -- may have a stronger scientific basis. Both dental extraction and endosseous implant placement may result in persistent pain, although the rates are unknown. This research project is not designed to support the superiority of tooth extraction and implant placement over non-surgical root canal treatment. Unless the rates of pain are very low, this research will likely support the notion that dental surgical procedures should be reduced when possible and/or preventive measures put in place in order to avoid the development of persistent pain. At the very least this research will influence the practice of dentistry by improving the information available for dentists and patients to make informed decisions.

Adequate treatments for some of these pains are emerging and appear to be more effective when patients are treated early in their course of pain (Vanotti et al., 2007). Early identification and treatment may improve prognosis, but the first step is to determine how widespread the problem is and how severely it affects the individual, as discussed above. Following this, the best next step towards improving care would be to identify at-risk individuals before root canal therapy is performed and intervene to prevent development of persistent pain and disability. For this to occur, the risk factors involved in development of persistent pain associated with root canal therapy need to be assessed before providing treatment. Potentially significant risk factors may be associated with the person (gender, tooth anatomy, psychosocial variables, medical health, concomitant medication use), disease (pulp/peri-radicular diagnosis), and treatment rendered (instrumentation and procedural difficulties, type of root canal provided). With the knowledge of these risk factors, dentists could reduce the potential for developing persistent pain by altering the course of treatment, such as pre-operatively modifying factors that are associated with high risk as well as implementing preventive strategies to neutralize factors that may not be modifiable. In this way this new knowledge will create a foundation for future clinical research that will further improve root canal therapy, and possibility other surgical dental procedures as well.

Even though this research proposal is focused on understanding the outcomes of root canal therapy, with the long-term goal of improving care, the resultant data may have ramifications for surgical procedures performed elsewhere in the body. Undoubtedly aspects of this research will be specific to root canal therapy, but since pain is a centrally derived phenomenon that affects the whole individual, aspects of the involved pain mechanisms are likely shared with other surgical procedures. Thus, this line of research could have an impact on healthcare in general. The profession of dentistry has repeatedly set a precedent of advancing the field of clinical pain management, with the discovery of general anesthesia (Calverley, 1996) and the development of the third-molar extraction model for acute-pain model (Averbuch & Katzper, 2003; Barden et al., 2004). This proposed research project affords the opportunity for dentists to play a role in better understanding the occurrence of persistent pain associated with surgical procedures; thereby continuing the advancement of clinical pain management.

C. PRELIMINARY STUDIES

Data from previous studies regarding pain associated with root canal therapy have been referred to in Section B above. A meta-analysis recently published in abstract form suggests that pain present 6+ months following root canal therapy occurs in 6% of treated teeth (95%CI=4-8%) (Moana Filho et al., 2008). This study identified 18 articles that met the inclusion criteria, 2 in non-English journals, from 463 articles published between 1950 and

2007. Overall, 5,158 teeth enrolled in the various studies, with 51% of those teeth followed to 6+ months (ranging=24-100%), yielded 152 teeth that were reported to have persistent pain.

Pilot studies on this topic have not been performed within the DPBRN, but prior experience within the DPBRN has shown that:

- Private practitioners in this network can be engaged and readily participate in research projects;
- Practitioner and patient recruitment has exceeded initial goals and does not limit completion of protocols;
- Regional coordinators can implement all aspects of research protocols (*e.g.*, obtaining ethical 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.

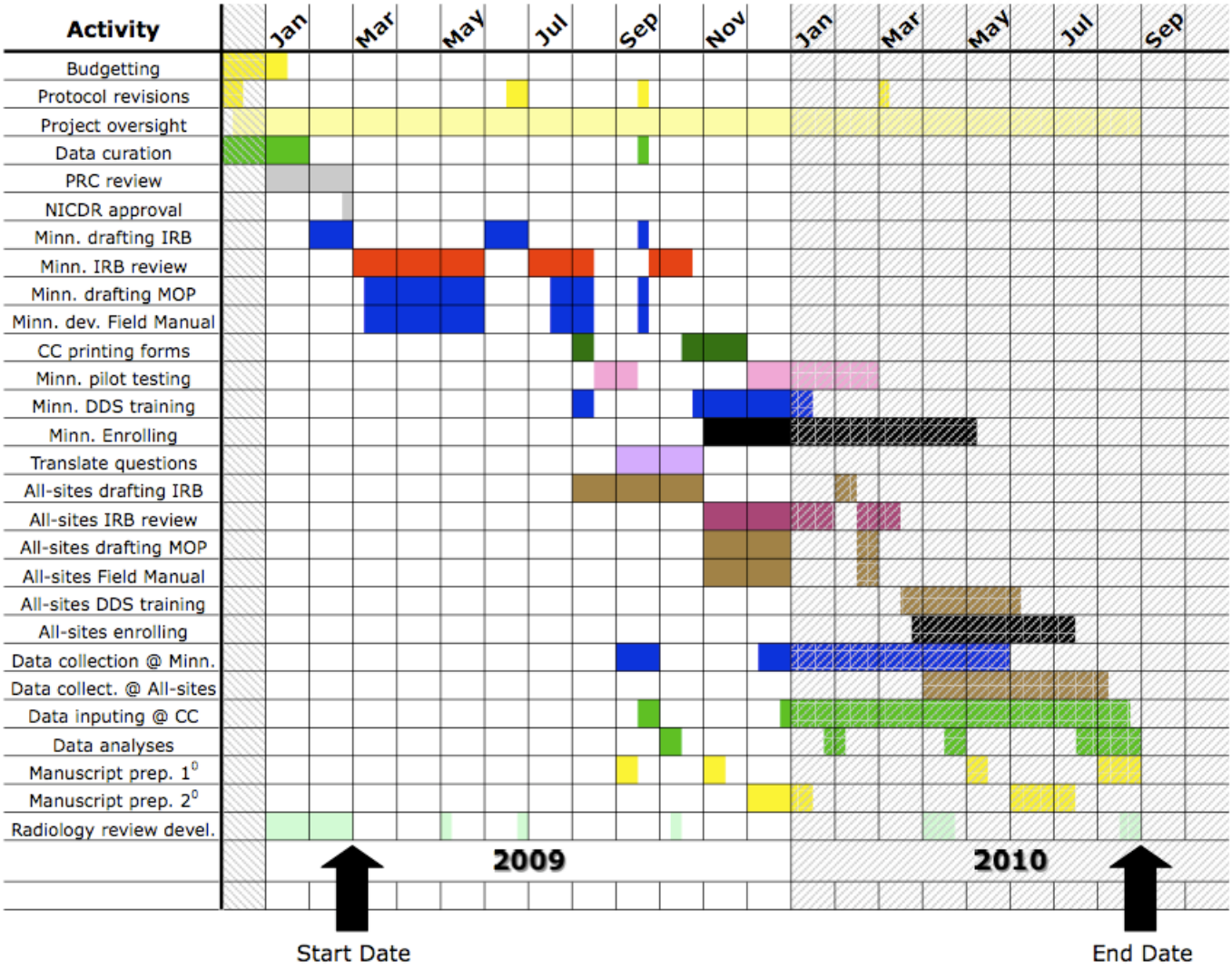
D. RESEARCH DESIGN and METHODS

D.1. Overview

In this longitudinal study, the 600 patients enrolled in the 'Peri-operative Tooth Pain' study within the DPBRN will be asked to complete a 10-item questionnaire 6 months after initiation of the root canal procedure. Completion of the mailed version of this questionnaire is expected to take the patient 3 minutes (telephone administration will take 10 minutes, e-mail administration 1 minute). To assist in follow up, patients will be sent a reminder at 3 months after root canal therapy. The primary outcome measure of persistent tooth pain is defined by an answer of ≥1 day(s) to "*On how many days in the last one month have you had tooth pain in the root canal treated tooth?*" from the GCPS questionnaire. All patient-teeth enrolled will be followed, regardless of the condition or presence of the tooth. Data collected by DPBRN study #11a will be used to assess risk factors for the primary outcome of persistent tooth pain.

Forty patients from the Minnesota region will come in for a follow-up clinical evaluation to assess the feasibility of obtaining sufficient numbers of patients to be re-evaluated and to assess the quality of periapical radiographs. Data regarding time to obtain this information will be collected to assess the feasibility of implementing this detailed data collection protocol. These data will be mailed to the regional coordinator using pre-addressed and stamped envelops, unless it is obtained by telephone conversation or e-mail.

Study Timeline



D.2. Patient recruitment and feasibility

All 600 patients enrolled in the 'Peri-operative Tooth Pain' study will be asked to participate in this study. Consent specific to this study will be obtained. This will include information about being reminded at 3 months and contacted at 6 months following root canal therapy. We anticipate a 17% drop out rate from the patient group enrolled in the 'Peri-operative Tooth Pain' study. Thus, our expected sample size is 500 patients.

D.3. Outcome measures

All data for the first set of aims will be obtained by use of a questionnaire. The **primary outcome measure of persistent tooth pain** is defined by an answer of ≥1 day(s) for "*On how many days in the last one month have you had tooth pain in the root canal treated tooth?*" from the GCPS (see **Appendix 1**). The GCPS is a reliable and valid pain measurement tool used extensively in epidemiological studies (Von Korff et al., 1992; Smith et al., 1997; Von Korff, 2001). **Pain intensity** is defined in this instrument by, "*In the past one month, on average, how intense was your tooth pain rated on a 0 to 10 scale?*" Other items of the GCPS assess **pain interference in daily life**.

Several **potential risk factors**, obtained within the 'Peri-operative Tooth Pain' study will be used to assess correlations with the outcome of persistent 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)

D.4. Data collection.

Three months after initiation of root canal therapy, all enrolled patients will receive a 2-item follow-up mailing from the Regional Center (see **Appendix 1**). The mailing, or other preferred method of communication, will ask patients to report any changes to their address or telephone number and to answer a single question about persistent pain: "Are you experiencing pain in the area of the tooth that was treated with the root canal?"

Six months after initiation of root canal therapy, patients will complete the 10-item follow-up questionnaire (see **Appendix 1**; estimated 3 minutes to complete). Patients will mail their completed questionnaire to the regional coordinating center via a self-addressed pre-paid postage envelope provided in the mail-out package.

Besides the 3-month reminder, a reminder telephone call (or e-mail if that is the preferred method of communication) will be sent by each 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 7 business days following the due date, a second reminder message will be sent to the patient that includes the 10 items from the questionnaire. At 2 weeks past the due date, a third and final reminder message will be sent to the patient by the regional coordinating center. The patient will be considered lost to follow-up if the third reminder garners no response.

If the tooth was extracted or received other treatment sometime after root canal therapy but before completion of the study, data collection will still proceed as outlined above.

Comprehensive version of data collection protocol

To pilot test the feasibility of the more comprehensive questionnaires, only the 4 Minnesotan practitioner-investigators who enrolled 40 patients will need to have re-evaluation appointments with their patients. During this appointment, the dentists will complete a more detailed data collection protocol that consists of 19 items (see **Appendix 2**). The dentists will also have to submit 6-month follow-up periapical radiographs. The 4 practitioner-investigators will be chosen to represent the various practice types present within the DPBRN, *i.e.* general *vs*. specialty practice and private *vs.* corporate business structure. Attention will be paid to ensure that practices using film and digit 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 dentist's overall-all satisfaction with the data collection process, will be obtained and used to assess feasibility of implementing this more comprehensive data collection protocol.

D.5. 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 analysis will be performed by one member of the statistical consulting unit and subsequently verified by another, using the SAS® statistical software system.

D.6. Statistical analysis

Aim 1 is the primary study objective. The overall proportion of patients with persistent pain will be reported with a 95% confidence interval to indicate the precision of the estimate. Proportions will also be summarized for key subgroups such as those treated by endodontists, those treated by general dentists, males, and females. All proportions and confidence intervals will be calculated as crude proportions and repeated using logistic regression with generalized estimating equations (GEE) to account for clustering of patients within provider and region.

Patients will report outcome measure on a scale from 0 to 10 using questions from the GCPS. The presence of persistent pain (Aim 1.1) is defined dichotomously by the experience of any pain, ≥1/10 GCPS rating, at the 6-month follow-up. Interference with daily life (Aim 1.2) is dichotomous, defined as occurring for those patients who score grade III or IV, known as dysfunction grades, which by definition means they have some amount of pain. Aim 1.3 will explore the relationship between a limited number of risk factors from the data collected in study 11a with the outcome of having persistent pain, as well as having a dysfunctional grade of pain interference with daily life (i.e. III or IV). The approach will be to model the presence of persistent pain as a function of the previously measured pain variables, such as pre-operative pain rating, using logistic regression including GEE, as appropriate to account for clustering. This will then be repeated for the other variables, such as intra-operative pain and short-term flare-up pain. A second approach will use logistic regression to model the presence of persistent pain as a function of the limited number of variables from study 11a. The above analyses will then be repeated explicitly examining the effect of modifying variables, such as practitioner type (general dentist vs. endodontist), by including practitioner type as a covariate. There are likely important clinical reasons influencing the outcomes of root canal therapy when testing potential risk factors, such as reasons for referral regarding outcomes for general dentists and endodontists, so that tests must be interpreted with care.

The second group of aims will assess the feasibility of doing a study like this with comprehensive data collection. Aims 2.1 estimates the proportion of patient questionnaires completed and returned at 6 months, while Aim 2.2 estimates the number of patients who return for their 6-month re-evaluation appointment. These estimates will be calculated and reported with 95% confidence intervals both overall and separately by practitioner type. Aim 2.3) will rely on self-reports from study 11a's 40 Minnesota patients, 4 Minnesota dentists and the Minnesota regional coordinator to quantify how much time is required to complete the more comprehensive data protocol as piloted. These results will be presented as a mean with standard deviation and as a histogram. Aim 2.4 will estimate the proportion of periapical radiographs obtained during the 6-month re-evaluation appointment considered to be of diagnostic quality among the same pilot-testing cohort of forty patients and four practitioners.

These proportions will be reported with a two-sided 95% confidence interval. In addition, a list of reasons observed for insufficient radiograph quality will be compiled by the two independent raters for further consideration.

D.8. Sample size and power considerations

Determining the number of subjects required to estimate the proportion with persistent 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 3% to 12% (proportions of 0.035 to 0.12) of people undergoing successful root canal therapy subsequently develop persistent pain. For example, estimating the proportion of 1% with precision of +/- 1% requires 381 subjects while estimating a proportion of 13% with the same precision of +/- 1% requires 4,345 subjects. Fortunately, as the observed proportion increases, the precision can be less stringent. For instance, estimating a proportion of 13% with a precision of +/- 3% (range of 10 to 16%) 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. Columns 1 to 4 show that if the expected proportion is approximately from 1% to 10% the study will require from 381 to 3,458 subjects to estimate the proportion +/-1%. For high proportions it is no longer necessary for the estimate to be so precise. Columns 5 through 10 illustrate how reducing the precision impacts the required sample size: when the proportion is 10% a precision of +/-2% requires only 865 subjects while a precision of +/-3% requires 385 subjects. The most recent study of persistent pain after successful root canal therapy (Polycarpou et al., 2005) reported a proportion of 12%, as 21 out of a total of 175 subjects with a precision of +/-4.8%. That study's observed proportion is larger than the other studies' estimates, suggesting the possibility that more participants with persistent pain consented to follow-up. It therefore seems reasonable to base the sample size on an expected proportion between 3% and 10%, thus requiring fewer than 500 participants to measure the observed proportion with adequate precision. Indeed, the table below shows that there will likely be adequate precision to provide separate estimates for the groups of 300 patients treated by endodontists and general dentists. These power calculations do not account for clustering of patients within providers for two reasons. First, while we expect that by far the largest source of variability will be at the patient level, there is no available literature to suggest a reasonable estimate for the intraclass correlation and second, there will be few patients per provider, at least among the general dentists, thus leading to a small design effect.

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

	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**
Expected proportion (%)	1%	3%	3%	3%	5%	5%	5%	10%	10%	10%
Precision (+/- %)	1%	1%	2%	3%	1%	2%	3%	1%	2%	3%
Estimated sample size, n	**381**	**1118**	280	125	1,825	**457**	203	3,458	865	**385**

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.

Remuneration

The 4 practitioner-investigators who are to enroll subjects for pilot testing of recalling patients for a clinical evaluation with radiographs at 6-months will be remunerated $50 per completed set of questionnaires and radiograph returned to the regional coordinating center. 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. The practitioner-investigators will charge their normal fees for the treatment provided. Subjects will not be paid for their participation but will be remunerated ~~$30 when the final questionnaire is received by the regional coordinating center.~~ Patient subjects will receive "$10.00 gift card for each one-week survey completed after your root canal appointment(s)." One week after the RCT they fill out and return a short survey and we send the $10.00 gift card. If pt returns for further work for that same root canal, they fill out another survey one week after that visit and we send a second gift card, etc.). Patient subjects will receive a $10.00 gift card for returning a completed 3-month survey and will receive one $30.00 gift card for returning a completed 6-month survey.

From: Gregg H Gilbert [mailto:ghg@uab.edu]
Sent: Wednesday, June 10, 2009 3:47 PM
To: Joshua S. Richman
Cc: Andrea Mathews
Subject: RE: DPBRN - confirmation re reimbursement

Payments to **practitioner-investigators** for doing studies come from the NC budget and are paid by Andi Mathews.

Payments to **patients** are made by regional staff from the region's budget, *after a transfer of the budgeted amount from the NC budget to the region's subcontract*.

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 pain 6-months 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 work that will expand and refined these risk factors, as well as 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 dental community. The racial and ethnic distribution of dental practitioners expected to participate in the study.

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 on page 19 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: **Persistent 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

Allerbring, M., & Haegerstam, G. (1993). Characteristics of patients with chronic idiopathic orofacial pain. A retrospective study. *Acta Odontologica Scandinavica, 51*(1), 53-58.

Allerbring, M., & Haegerstam, G. (1995). Invasive dental treatment, pain reports, and disease conviction in chronic facial pain patients. A retrospective study. *Acta Odontologica Scandinavica, 53*(1), 41-43.

Allerbring, M., & Haegerstam, G. (2004). Chronic idiopathic orofacial pain. A long-term follow-up study. *Acta Odontologica Scandinavica, 62*(2), 66-69.

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

Averbuch, M., & Katzper, M. (2003). Severity of baseline pain and degree of analgesia in the third molar post-extraction dental pain model. *Anesthesia & Analgesia, 97*(1), 163-167.

Barden, J., Edwards, J. E., McQuay, H. J., & Moore, A. R. (2004). Pain and analgesic response after third molar extraction and other postsurgical pain. *Pain, 107*(1-2), 86-90.

Basmadjian-Charles, C. L., Farge, P., Boureois, D. M., & Lebrun, T. (2002). Factors influencing the long-term results of the endodontic treatment: A review of the literature. *International Dental Journal, 52*, 81-86.

Calverley, R. K. (1996). Anesthesia as a specialty: Past, present, and future. In P. G. Barash, B. F. Cullen & R. K. Stoelting (Eds.), *Clinical anesthesia* (Third ed., pp. 3-28). Philadelphia: Lippincott-Raven.

Campbell, R. L., Parks, K. W., & Dodds, R. N. (1990). Chronic facial pain associated with endodontic therapy. *Oral Surgery, Oral Medicine, and Oral Pathology, 69*(3), 287-290.

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.

Friedman, S., Abitbol, S., & Lawrence, H. P. (2003). Treatment outcome in endodontics: The Toronto study. phase 1: Initial treatment. *Journal of Endodontics, 29*(12), 787-793.

Friedman, S., & Mor, C. (2004). The success of endodontic therapy--healing and functionality. *Journal of the California Dental Association, 32*(6), 493-503.

Graff-Radford, S. B., & Solberg, W. K. (1986). Atypical odontalgia. *Canadian Dental Association Journal, 14*(12), 27-32.

Haegerstam, G., & Allerbring, M. (1995). Lack of disability in patients with chronic orofacial pain. a retrospective study. *Acta Odontologica Scandinavica, 53*(6), 345-348.

Harris, M. '. (1974). Psychogenic aspects of facial pain. *British Dental Journal, 136*(5), 199-202.

Hoskinson, S. E., Ng, Y., Hoskinson, A. E., Moles, D. R., & Gulabivala, K. (2002). A retrospective comparison of outcome of root canal treatment using two different protocols. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 93*, 705-715.

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

Jensen, T. S., & Nikolajsen, L. (1999). Phantom pain and other phenomena after amputation. In P. D. Wall, & R. Melzack (Eds.), *Textbook of pain* (4th ed., pp. 799-814). Edinburgh: Churchill Livingstone.

Kehlet, H., Jensen, T. S., & Woolf, C. J. (2006). Persistent postsurgical pain: Risk factors and prevention. *Lancet, 367*, 1618-1625.

Kojima, K., Inamoto, K., Nagamatsu, K., Hara, A., Nakata, K., Morita, I., et al. (2004). Success rate of endodontic treatment of teeth with vital and nonvital pulps. A meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 97*, 95-99.

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.

Lavigne, G. J., & Sessle, B. J. (2004). The Vancouver symposium: A unique focus on nerve damage and neuropathic trigeminal pain. *Journal of Orofacial Pain, 18*, 277-277.

Lobb, W. K., Zakariasen, K. L., & McGrath, P. J. (1996). Endodontic treatment outcomes: Do patients perceive problems? *Journal of the American Dental Association (1939), 127*(5), 597-600.

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.

Marbach, J. J., Hulbrock, J., Hohn, C., & Segal, A. G. (1982). Incidence of phantom tooth pain: An atypical facial neuralgia. *Oral Surgery, Oral Medicine, and Oral Pathology, 53*(2), 190-193.

Marbach, J. J. (1978). Phantom tooth pain. *Journal of Endodontics, 4*(12), 362-371.

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.

Moana Filho, E. J., Nixdorf, D. R., John, M. T., McGuire, L. A., & Law, A. L. (2008). Meta-analysis assessing persistent pain following root canal therapies [Abstract]. *Journal of Dental Research, 87*(Spec Iss B) 108474.

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.

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.

Rahbaran, S., Gilthorpe, M. S., Harrison, S. D., & Gulabivala, K. (2001). Comparison of clinical outcomes of periapical surgery in endodontic and oral surgery units of a teaching dental hospital: A retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 91*(6), 700-709.

Rees, R. T., & Harris, M. (1979). Atypical odontalgia. *British Journal of Oral Surgery, 16*, 212-218.

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.

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.

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

Vanotti, A., Osio, M., Mailland, E., Nascimbene, C., Capiluppi, E., & Mariani, C. (2007). Overview on pathophysiology and newer approaches to treatment of peripheral neuropathies. *CNS Drugs, 21*(Suppl 1), 3-12.

Von Korff, M. (2001). Epidemiologic and survey methods: Chronic pain assessment. In D. Turk, & R. Melzack (Eds.), *Handbook of pain assessment: Second edition* (Second Edition 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.