

Management of Painful Temporomandibular Disorders (TMD)

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STATEMENT OF COMPLIANCE

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

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

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The signature below constitutes:

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

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LIST OF ABBREVIATIONS

AAOP	American Academy of Orofacial Pain
AE	Adverse Event/Adverse Experience
CC	Coordinating Center
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
CONDOR	Collaboration on Networked Dental and Oral Research
DMP	Data Management Plan
DHHS	Department of Health and Human Services
FFR	Federal Financial Report
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
GPI	Grant Principal Investigator
HIPAA	Health Insurance Portability and Accountability Act
HP IDCC	HealthPartners Institute Data Coordinating Center
ICF	Informed Consent Form
ICC	Intraclass Correlation Coefficient
IRB	Institutional Review Board
MMOR	Medical Monitor Oversight Report
MOP	Manual of Procedures
N	Number (typically refers to participants)
National Dental PBRN	National Dental Practice-Based Research Network
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PD	Protocol Deviations
QA	Quality Assurance
QC	Quality Control
QM	Quality Management
RAS	Regional Administrative Site
RC	Regional Coordinator
SAE	Serious Adverse Event/Serious Adverse Experience
SD	Source Documents
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure

PROTOCOL SUMMARY

- Title:** **Management of Painful Temporomandibular Disorders (TMD)**
- Précis:** Temporomandibular Disorders (TMD) are the second most commonly occurring musculoskeletal disorders after chronic back pain resulting in pain and disability. Diagnosis and treatment of TMD are within the purview of general dentistry (NIDCR, 2009) with most patients consulting a general dentist regarding their painful TMD. Within the context of the National Dental Practice-Based Research Network (Network), the goal of this observational prospective cohort study is to identify factors contributing to TMD treatment decisions and treatment adherence, as well as the overall effect of TMD treatment on pain intensity and jaw function measured at 1-, 3- and 6-month follow-ups. We will recruit approximately 200 dentist practitioners from the six National Dental PBRN regions (Northeast, South Atlantic, South Central, Southwest, Midwest, Western). Each participating dentist will contribute to a total patient enrollment of approximately 1980.
- Objectives:** The primary objective of this study is to identify the factors that contribute to practitioners' treatment decisions for patients with painful TMD.
- The secondary objectives of this study are to:
- 1) Identify factors that contribute to patients' adherence to treatment, and
 - 2) Describe observed changes from baseline at 1-, 3- and 6-month follow-up in pain intensity and jaw function associated with treatments.
- The primary outcome measure of this study is the practitioners' treatment decisions for painful TMD patients. The secondary outcome measures for this study are patient adherence, and pain intensity and jaw function measures. Numerous potential confounders and predictors will be assessed for their associations with the treatment decisions, patient adherence, and changes in pain and function.

- Population:** The study will include approximately 1980 adult patients with painful TMD, age ≥ 18 years (except in Nebraska where consent is age ≥ 19 years) who agree to be treated for their painful TMD in a participating Network practice.
- Number of Sites:** Approximately 200 National Dental PBRN dentists will be recruited into the study from the six Network regions.
- Study Duration:** Approximately 30 months.
- Subject Participation Duration:** Approximately 12 months (practitioner).
Approximately 6 months (TMD patients).
- Estimated Time to Complete Enrollment:** Enrollment of practitioners = 18 months per region.
Enrollment of patients = 21 months per region.

Schematic of Study Design:

Practitioner
Enrollment

N = Approximately 200 Participating National Dental PBRN **practitioners** complete informed consent, per regional IRB requirements. RCs train practitioners and their staff/personnel.



Study Visit
1 (Patient
Enrollment)

Patient presents at participating practice with jaw or temple pain and is seeking treatment for this complaint. **Practitioner** obtains history, performs initial assessment, renders painful TMD diagnosis, and proposes TMD treatment plan. **Patient** agrees to move forward with the proposed treatment. **Practitioner or office staff** assesses study inclusion and exclusion criteria, explains study requirements. **Patient** provides informed consent, per regional IRB requirements, and is enrolled in study.



Study Visit
1 (Baseline)

N = Approximately 1980 TMD pain patients:
Patient completes the Patient Contact Form, Patient Demographic Form and the Initial Patient Questionnaire.
Practitioner completes the Initial Doctor Questionnaire.



Follow-up at
1 month +2
weeks

At 1-month follow-up:
Patient completes the Patient Follow-up Questionnaire at one month post baseline.



Follow-up at
3 and 6
months ± 2
weeks

At 3- and 6-month follow-ups:
Patient completes the Patient Follow-up Questionnaire at 3- and 6-months post baseline.
Practitioner completes the Doctor Follow-up Questionnaire at 6 months post baseline.



The primary data analysis will identify factors influencing treatment selection, factors associated with patient treatment adherence and, for any TMD treatment, the overall observed changes in patients' pain intensity and jaw function at follow-up. This analysis will utilize generalized linear models, implemented with generalized estimating equations (GEE) in order to account for correlation among observations on multiple patients of the same dentist.

1 KEY ROLES AND CONTACT INFORMATION

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Temporomandibular disorders (TMD) are the second most commonly occurring musculoskeletal disorders after chronic back pain resulting in pain and disability. It has been estimated that approximately 5-12% of the US population is affected by painful TMD and approximately half to two-thirds will seek professional care, with an annual cost estimated at \$4 billion dollars (NIDCR, 2009). A recent systematic review regarding current TMD treatments for chronic painful TMD subjects concluded that “there is some evidence that the following can be effective in alleviating painful TMD: splints, acupuncture, behavioral therapy, jaw exercises, postural training, and some pharmacological treatments” (List and Axelsson, 2010; p. 430). However, the review concluded that considerable variation in methodology, and the outcomes reported between the primary studies made definitive conclusions impossible. Further, there is uncertainty about whether treatment outcomes differ for patients with acute compared to chronic TMD pain.

Diagnosis and treatment of TMD are within the purview of general dentistry (NIDCR, 2009) with most patients consulting a general dentist regarding their painful TMD. Drs. Schiffman and Velly performed a survey with the Collaboration on Networked Dental and Oral Research (CONDOR), a consortium of the three prior dental PBRNs (Velly et al, 2013). This survey showed that 94% of the general dentists surveyed use both a history and an exam protocol to diagnose TMD pain. Of the 654 dentists surveyed, 525 (80%) were willing to participate in a study to assess the success of current treatments for TMD pain. These 525 dentists treat an average of 3 TMD pain patients per month (95%CI: 2.7-3.4), with the most frequent treatments being splint therapy (98%), over the counter or prescription medications (85%), self-care (86%), occlusal adjustment (64%) and exercises (53%). Dentists indicated that these treatments were not always effective (overall $\leq 15\%$). They also indicated that the greatest difficulties with these treatments were the time required to implement them (overall $\leq 14\%$), and patient cost (overall $\leq 17\%$). Finally, dentists reported that some patients are non-compliant with treatments (overall $< 25\%$).

Numerous factors are associated with practitioner treatment selection; these factors can be categorized as clinician/practice-related factors, and patient-related factors. In the CONDOR survey, dentists selected specific treatments based on the expectation they are effective for reducing pain: splint (64%), self-care (65%), medication (64%), occlusal

adjustment (65%), and exercises (64%) (Velly et al, 2013). Furthermore, dentists often used more than one treatment such as self-care and splint therapy. The CONDOR study also revealed patient acceptability, anticipated treatment compliance, cost and side effects as patient-related factors that influence treatment selection.

Turk and Rudy (1991) noted that non-adherence with treatment regimens was widespread across diverse treatment modalities and pain syndromes. One study on adherence among pain patients relates to medication use in which underuse was reported to vary from 8% to 52% and overuse from 4% to 21% (Broekmans, 2009). Another study assessed predictors of adherence to a range of TMD treatments in 80 chronic TMD patients and reported that measures of psychological distress and pain were predictive of greater overall adherence (Riley *et al.*, 1999). Further, depression was negatively associated with compliance to recommended medication changes, therapeutic injections, and splint therapy, but not negatively associated with compliance with psychological counseling or physical therapy. Painful TMD patients often have episodic exacerbations, and several studies have found that patients' motivation to adhere to treatment may diminish between exacerbations (Rains *et al.*, 2006; Medina-Mirapies *et al.*, 2009). Other patient variables shown to be associated with increased treatment adherence include older age, female sex and beliefs that therapy will help (Raines *et al.*; 2006; Viller *et al.*, 2000; Broekmans. 2009).

The purpose of this study is to characterize the factors contributing to treatment decisions, patient adherence to treatment, and the overall effectiveness of a broad spectrum of treatments employed in the dentist-based clinical care setting of the Network. Differential predictors of treatment outcome will be assessed in acute and chronic TMD pain patients.

2.2 Rationale

As discussed above, there is a lack of evidence regarding the overall effectiveness of TMD pain treatments in the clinical care setting, as well as the factors that contribute to positive outcomes. Treatment effectiveness may be defined and understood in terms of measurable reduction in TMD pain intensity and improvement of jaw function. In addition, there is a paucity of research to advise dentists about the possible differential influence of these outcomes in patients with acute versus chronic TMD pain. Limited data also exist about factors associated with treatment selection for TMD pain and with treatment adherence by the patient.

This study will provide evidence to help dentists advise and educate their patients about factors affecting their treatment outcome within the context of the Network. Given the distribution of the Network dentists across the United States and the educational outreach of the Network to the dental profession, these findings should have a widespread impact on TMD treatment in dental practices.

2.3 Potential Risks and Benefits

There are no anticipated human subject safety risks to participating in this study. Research participants will not receive dental care as a study procedure, but will continue to receive normal clinical care as patients of the participating dentists. Risks of dental treatment provided as part of normal clinical care are not considered to be study-associated.

2.3.1 Potential Risks

As with any study, there is the possibility of breach of confidentiality. Appropriate precautions will be taken and procedures will be followed to maintain confidentiality. These include use of unique study codes for participants, encryption of electronic data for transmission to the HealthPartners Institute Data Coordinating Center (HP IDCC), and password-protected computers for data storage. Compliance with all IRB regulations concerning data collection, data analysis, data storage, and data destruction will be strictly observed.

2.3.2 Potential Benefits

Participation in this study will provide no direct benefit to patients. The potential benefits of this study are that the results may allow dentists to have a better understanding of how to more appropriately assess, triage and/or treat TMD pain patients. The results may benefit the dental profession and TMD pain patients so that appropriate healthcare advice and care can be provided to patients in the future.

3 OBJECTIVES

3.1 Study Objectives

The primary objective of this study is to identify practitioner- and patient- based factors that contribute to practitioners' treatment decisions for patients with TMD pain.

The secondary objectives of this study are to:

- 1) Identify factors that contribute to patients' adherence to treatment, and
- 2) Describe observed changes from baseline in pain intensity and jaw function associated with TMD treatment.

3.2 Study Outcome Measures

Objectives	Outcomes	Instrument	When assessed
Primary Objective	Treatment decisions outcomes (binary data): <ul style="list-style-type: none"> • Treatment indication versus referral to an expert; • Treatment implemented: <ol style="list-style-type: none"> a) self-care, b) medications, c) appliance therapy, d) occlusal adjustment, e) home exercises, f) other, and g) combination (multimodal) treatments. 	Initial Doctor Questionnaire	Baseline
		Doctor Follow-up Questionnaire	Follow-up***
Secondary Objective 1	Patient adherence to treatment (binary data)	Patient Questionnaire: One-Month Follow-up	Follow-up*
		Patient Questionnaire: Three- and Six-Month Follow-up	Follow-up**
		Doctor Six-Month Follow-up Questionnaire: Practitioner's assessment of treatment adherence.	Follow-up***
Secondary Objective 2	Change from baseline in the intensity of pain and jaw function (both continuous data)	Initial Patient Questionnaire (baseline levels of outcome variables)	Baseline
		Patient Questionnaire: One-Month Follow-up	Follow-up*
		Patient Questionnaire: Three- and Six-Month Follow-up	Follow-up**
* 1-month patient follow-up ** 3- and 6-month patient follow-ups *** 6-month doctor follow-up			

Primary Objective Predictors

The following potential predictors will be assessed for their association with the practitioners' treatment decisions:

Practitioner/practice predictors: Dentist's belief that treatment(s) are effective, experience with implementing TMD treatments, time required to implement treatment, cost of treatment, whether patients have insurance coverage for treatment, and whether the dentist believes that the patient will be compliant with his/her treatment recommendations. Dentists will also rate their perspective of the patient's viewpoint, in addition to their own, regarding treatment effectiveness, acceptability, and side effects. Finally, potential predictors for treatment recommendations are the dentist's demographics (e.g., age, sex), years of practice, and specialty, which will be obtained through the National Dental PBRN Enrollment Questionnaire.

Secondary Objective 1 Predictors

The following potential predictors will be assessed for their association with patient adherence:

Practitioner/practice predictors: practitioner's expectation of patient's acceptance of treatment, practitioner's expectation of effectiveness of treatment to decrease pain, and practitioner's ratings of patient's understanding of treatment plan.

Patient-based predictors: number of previous TMD pain treatments, patient's belief in recommended treatment's effectiveness, patient's comprehension of the treatment plan, satisfaction with the treatment plan, ease of implementing treatment recommendations, patient's rating of the practitioner's communication, treatment side effects, and ongoing cost.

Secondary Objective 2 Predictors

The following putative confounders for treatment success will be assessed for their association with observed change-from-baseline in pain intensity and jaw function: psychological distress (including anxiety and depression), sleep quality, oral habits, presence of co-morbid or widespread pain, headache experience, and pain-related disability, pain frequency and chronicity of painful TMD. This study will also assess patient's treatment preference, treatment difficulty of use, treatment side effects, age, sex, health condition, education, and insurance coverage.

4 STUDY DESIGN

- **Study design.** This is a prospective cohort observational study of practitioners and patients in the Network. The prospective cohort design will allow the investigation of how practitioner, practice, and patient factors contribute to treatment decisions, patient adherence, and change in pain intensity and jaw function over time.
- **Study population.**
 - **Practitioners.** Approximately 200 Network practitioners from the six Network regions who treat TMD will be recruited in this study. This sample will be recruited to provide the necessary information to assess the primary objective and secondary objective 1. This recruitment permits up to a 10% practitioner withdrawal from participation, with a goal of having 180 practitioners complete the study.
 - **Painful TMD patients.** Approximately 1980 acute and chronic painful TMD patients, who will receive TMD treatment from a Network dentist, will be invited to participate in this study, even if they had previous TMD treatment. This sample will be recruited to provide the necessary information to assess all study objectives. Recruitment of approximately 1980 patients allows for at least an 80% target retention rate, or 1584 patients who complete the study.
- **Data collection:** Consent will be administered via paper and data will be collected via electronic means for the study. Patient-reported data will be collected via tablets, smart-phones, or computers during in-office visits and other time points. To assist with in-office data collection, practitioner participants will be offered tablets. Practitioners will provide clinical examination and procedural data electronically via tablets, smart-phones, or computers. Follow-up contacts to non-responders will be managed by the HP IDCC.

Overview of Study Schedule

- Practitioners will enroll in the study and provide consent according to regionally approved procedures; the practitioner and office staff will receive study training provided by the Regional Coordinator (RC). Then the practitioner is authorized to begin enrolling study participants.
- To determine if a patient meets the criteria for study inclusion, the patient must indicate having painful TMD. After the practitioner makes a diagnosis of the presence of painful TMD, utilizing diagnostic criteria s/he uses in clinical practice (e.g. history and exam), and the patient accepts the treatment plan, the staff/personnel may enroll the patient into the study. The practitioner is not required to ask any specific history items or perform any specific exam

procedures other than those s/he usually implements to make a diagnosis of painful TMD.

- After consenting to study participation, study patients will complete baseline questionnaires: Patient Contact, Patient Demographics and *Initial Patient Questionnaire* and then will complete follow-up assessments at 1-, 3-, and 6-months post-baseline visit via an online questionnaire. Initial non-responders will be followed up with email, telephone and/or text attempt.
- The practitioners will complete at baseline the *Initial Doctor Questionnaire*.
- While there is no study-required in-office treatment follow-up visit, it is likely that most TMD patients will undergo follow-up visits with the practitioner as a part of their treatment. If the patient returns for evaluation by the practitioner, the practitioner is requested to assess treatment adherence during the elapsed time since the baseline visit, and record any change in painful TMD diagnoses or treatment procedures. This is reported on the 6 month *Doctor Follow-up Questionnaire*.
- The Study Team has implemented pilot testing of the practitioner and patient questionnaires to assess length and acceptability. The Study Team has refined the questionnaires based on RCs, executive committee members, practitioner and patient feedback. The electronic data system used to collect patient and practitioner data will be assessed for acceptability and compatibility prior to administration of questionnaires.

First Month Follow-up of Study Patients by Study Staff

Patient participants will receive emails with active links to the online web-based one-month *Patient Follow-up Questionnaire* for electronic completion. The HP IDCC will attempt email, telephone and/or text contact for non-responders to remind them to complete the questionnaires online or over the telephone. Completion of form over the telephone is an option that will remain available for those patients who do not complete the form by close of data collection window.

Months 3 and 6 Follow-up of Study Patients by Study Staff

Similar procedures, as in the first month of follow-up, will be repeated in months 3 and 6.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

Practitioner: In order to be eligible to participate in this study, a practitioner must be deemed study ready by their Regional Administrative Site (RAS) and meet the following criteria:

- Willing to provide consent according to regionally approved procedures;
- Has treated patients for TMD pain during the past year;
- Has the ability to receive emails and access online surveys.

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

- Willing to provide consent according to regionally approved procedures;
- Willing to comply with all study procedures and be available for the six month duration of data collection;
- Age \geq 18 years, except in Nebraska where consent is age \geq 19 years;
- Report of jaw or temple pain occurring in the last month;
- Diagnosis of painful TMD rendered by the practitioner;
- Seeking TMD treatment from the practitioner and accepting recommended treatment plan;
- Has the ability to receive emails, phone calls and access online surveys;
- Willing to be contacted as needed by each of these entities: the practice, Regional Coordinator (RC), and the HP IDCC;
- Willing to provide contact information for one other person who will know the patient's whereabouts in the event the patient cannot be reached. This contact information must be different from the patient's contact information.

5.2 Subject Exclusion Criteria

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

- Presence of pain-related dental pathology;
- Inability to understand study procedures or provide consent in English or Spanish.

5.3 Strategies for Recruitment and Retention

5.3.1 Practitioner Recruitment

Approximately 200 practitioners will be recruited to achieve the goal of having at least 180 dentists complete the study after allowing for a possible 10% dropout rate. All Network dentist practitioners who treat painful TMD patients will be approached for interest in participating in the study. The sampling frame of dentists will be created from lists of the Network participants. The study team will coordinate the recruitment plan and will rely on the RC from the six RAS to help recruit practitioners into the study. Practitioners will complete the *Practitioner Demographics Questionnaire*, which includes TMD experience and TMD training/professional organizations.

Practitioners will be compensated for the time required to do the research. Completion of the *Initial Doctor Questionnaire* for each enrolled patient is required in order to receive remuneration. For practitioners who enroll patients and complete the *Initial Doctor Questionnaire* for each enrolled patient, remuneration will include retaining the electronic data capture device used for patient data collection. Practitioners who enroll and complete the *Initial Doctor Questionnaire* for more than 6 patients will receive \$50 for each subsequent patient enrolled. In addition, practitioners will be compensated \$20 upon completion of each 6-month Doctor Follow-up Questionnaire.

5.3.2 Patient Recruitment

We will attempt to enroll approximately 1980 patients in approximately a 21-month period. To meet this patient recruitment goal, each participating practitioner will be asked to recruit a target of approximately 11 consecutive consenting patients with a maximum of 20 patients. Practices should be able to meet the recruitment goal by enrolling at a rate of approximately 1 patient per month. However, practitioners may enroll patients at a rate that best suits their practice situation. RCs will have access to the online study portal, where they will be able to monitor patient enrollment for practitioner study participants.

All painful TMD patients presenting at participating Network practices may be considered for eligibility after identification by the practitioners and/or trained office staff. Designated office personnel will introduce the study to patients who meet the inclusion criteria when they are seen for a dental appointment. For patients who meet eligibility

criteria and express an interest in study participation, a designated human subjects protection trained person will perform informed consent procedures.

Each office should have the latitude to designate tasks to office personnel in a manner that will work best within the normal operations of the practice. All study related documentation distributed to patients will be available in English and Spanish. Patients will be informed that *their* practitioners will be blinded to all responses on their baseline and follow-up questionnaires. *Other* office staff are permitted to assist patients with baseline questionnaires, and patients will be informed that their responses will not be shared with other personnel in the office. Patients will be informed that office staff, *in addition to their practitioners*, will not have access to their responses in the patient follow-up questionnaires.

5.3.3 Patient Retention

Patient retention is important to this study, and follow-up data will be collected independently of in-office visits. The patient retention plan is presented in Appendix B. Study patients will be asked to complete follow-up assessments online at 1-, 3-, and 6-months after the baseline visit. Patients will be paid \$125 total for completed questionnaires; \$25 at baseline, \$25 at 1-month follow-up, \$25 at 3-month follow-up and \$50 at the 6-month follow-up.

Study patients will be contacted by email prior to each follow-up data collection interval. The initial email contact for each survey period will contain the request to complete the questionnaire and an active link to the online web-based questionnaire. Email, telephone and/or text follow-up attempts will be implemented for non-responders. The HP IDCC will email, call and/or text patients who do not complete the follow-up questionnaires by the close of data collection window to encourage them to complete surveys. When contacted, patients will be given the option to complete the questionnaire by telephone with the coordinating center (CC).

5.4 Subject Withdrawal

5.4.1 Reasons for Withdrawal

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

An investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.

- The patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation. This criterion includes patients who complete the study who may be excluded from the data analysis.

5.4.2 Handling of Subject Withdrawals

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

Replacement of patients who withdraw or discontinue the study will be allowed, but only during the patient enrollment period. The practitioner may continue to enroll one patient for each enrolled patient who withdraws or discontinues during the practitioner-specific enrollment period.

5.5 Premature Termination or Suspension of Study

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

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

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data not sufficiently complete or evaluable.
- Determination of futility.

6 STUDY SCHEDULE

Practitioners enrolled in the National Dental PBRN who express an interest in the study and meet eligibility criteria will be invited to participate. Study information and instructions will be provided by regional staff to interested practitioners. A detailed Practice Training Manual will be provided to each practice prior to initiation of the study in the practice. The Practice Training Manual will carefully describe the patient selection procedures, methods for approaching patients and obtaining Informed Consent (according to regional approvals), methods for data collection, and other study procedures. In addition, RCs will conduct in-person or remote protocol training with office staff prior to initiating the study to make sure that practitioners and their office staff understand the study procedures and have received instruction in the consent process and the electronic data capture (EDC) system. The RCs will be in close contact with practitioners prior to and throughout study implementation to ensure that the practitioner and his/her office staff are familiar with study procedures.

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

- 1) Each region will enroll practitioners into the study to obtain a total of approximately 200 practitioners across all regions;
- 2) Practitioners will complete activities to be deemed study ready;
- 3) Once practitioners are study ready, RCs will ensure practices are trained in the appropriate study procedures;
- 4) Practitioners will screen and enroll eligible patients into the study.

The CC along with the RAS and RCs will coordinate the launch of the study. Once the RC has trained an enrolled office on study procedures, that practice should begin recruiting patients into the study immediately, or as soon as possible.

6.1 Practitioner Enrollment/Baseline

- Verify practitioner inclusion criteria;
- Obtain and document consent from practitioner participant according to regional IRB requirements; and
- Practitioner and applicable staff participate in study specific training with RC.

6.2 Patient Screening

A prospective study patient may be recruited at any dental appointment in a participating practitioner's dental office. There is no formal screening protocol required for this study other than the usual diagnostic procedures (history and exam) that the participating dentist would customarily employ for a patient who presents with jaw or temple pain. If the practitioner renders a diagnosis of painful TMD and proposes

treatment that is acceptable to the patient, the practitioner or practitioner's staff may introduce the study to the patient. Enrollment and baseline study procedures may occur at the same dental visit at which eligibility is confirmed or at a subsequent visit. The procedures listed below are consistent with those included in the Schedule of Events (Appendix A).

6.3 Patient Enrollment/Baseline

If eligible and interested in study participation, the patient will undergo consent procedures. A designated office staff member, most likely the dentist, will execute the regionally-approved consent process according to regional IRB requirements.

If an enrolled patient declines to provide any of the essential baseline data (collected confidentially) on the Patient Contact Form, the Patient Demographics Form, and/or the Initial Patient Questionnaire, this decision will be considered a voluntary withdrawal from the study by the patient.

Enrollment/Baseline Visit (Visit 1, Day 0)

- Verify patient inclusion/exclusion criteria.
- Verify and document consent from patient according to regional IRB requirements.
- Verify and document HIPAA authorization for use of the patient's Personal Health Information (PHI) in Research, based on regional IRB requirements.
- Obtain patient contact information and method of contact for electronic data capture.
- Patient completes Patient Contact questionnaire, Patient Demographics questionnaire and *Initial Patient Questionnaire*. If not completed at the baseline visit, the *Initial Patient Questionnaire* will be completed within approximately one week of baseline visit either online or via telephone interview with the CC.
- Record results of TMD examinations from practitioner on *Initial Doctor Questionnaire*.
- Record treatment recommendations and treatment prescribed/administered from practitioner on *Initial Doctor Questionnaire*.

6.4 Intermediate Follow-up Assessments

Follow-up Assessment 1 at 1 Month (+ 2 weeks)

- Patients will complete *Patient One-Month Follow-up Questionnaire* one month post baseline

Follow-up Assessment 2 at 3 Months (\pm 2 weeks)

- Patients will complete *Patient Three-Month Follow-up Questionnaire* 3 months post baseline

6.5 Final Study Assessments

Follow-up Assessment 3 at 6 Months (\pm 2 weeks)

- Patients will complete *Patient Six-Month Follow-up Questionnaire* 6 months post baseline
- Practitioners will complete *Doctor Follow-up Questionnaire* 6 months post baseline for all patients by close of the final data collection window.

6.6 Withdrawal Visit

- Record date and reason for withdrawal.
- Consistent with Section 5.4.2, the only evaluations and data collection authorized will be information needed to address an unanticipated problem or other safety issue that may have led to his/her withdrawal from the study.

6.7 Unscheduled Visit

Any change in diagnosis or treatment that occurs during a scheduled or unscheduled follow-up visit at any time during the duration of patient study participation will be reported in the 6 month *Doctor Follow-up Questionnaire*, along with the requested estimate of patient treatment adherence.

7 STUDY PROCEDURES/EVALUATIONS

The intent of this observational study is to observe usual clinical care and not to influence or manipulate the normal standard of clinical care offered by the participating dentists, including the practitioner's preferred methods for diagnosis and treatment of painful TMD.

7.1 Study Procedures/Evaluations

Enrollment. For each patient enrolled, the practitioner will complete an *Initial Doctor Questionnaire* based upon their usual clinical examination and patient history recording: 1) patient's pertinent medical/dental history; 2) patient's chief complaint (practitioner perspective); 3) clinical TMD pain and function assessments; 4) other diagnostic modalities utilized; 5) diagnosis of painful TMD; 6) treatment plan recommendations; 7) anticipated patient acceptance of treatment; 8) anticipated cost of treatment; and 9) anticipated treatment result and difficulties.

After patient consent, the patient will complete a *Patient Contact Form, Patient Demographics Form and Initial Patient Questionnaire*, which will ascertain: 1) patient contact information, sex, birth date, ethnicity, race, insurance coverage, education, marital status, income, number in household, zip code; 2) jaw temple pain location, duration, intensity, pain-related disability, pain frequency and chronicity; 3) pain-related symptoms and contributors to pain; 4) number of healthcare providers seen for jaw temple pain; 5) jaw functional limitation; 6) headache experience; 7) oral habits, sleep quality, presence of widespread pain; 8) anxiety/depression, emotional coping; 9) general health, and 10) treatment-related expectations and satisfaction.

One-month follow-up. The patient will complete the *Patient One-Month Follow-Up Questionnaire*, recording: 1) jaw temple pain location, duration, intensity, pain-related disability; 2) number of days with headache; 3) jaw functional limitation; 4) change in pain, functional limitation; 5) satisfaction with treatment, ease of implementing treatment; 6) understanding of recommended treatment and why it was recommended; 7) self-efficacy for prognosis; 8) adherence to treatment recommendations; and 9) treatment-related contribution to change in pain, side effects.

Three- and six- month follow-up. The patient will complete the Patient Three- and Six-Month Follow-Up Questionnaires, which ascertain: 1) measures of communication with the practitioner; 2) treatment-related changes in TMD pain and jaw function; 3) treatment difficulty, side effects; 4) adherence to treatment recommendations.

Practitioner 6-month follow-up. The practitioner will complete the *Six-Month Doctor Follow-up Questionnaire* for patients who undergo follow-up in-office visits with the practitioner, including: 1) any change in diagnosis or treatment recommendations; 2) patient adherence to treatment (practitioner perspective).

7.2 Questionnaire Administration

Development of data collection instruments

With guidance from NIDCR, questionnaire development has included refinement of data collection instruments with an emphasis on reducing overall burden and improving acceptability. Questionnaires have been developed from validated instruments, when possible, that have been modified and/or combined with other instruments. Consequently, cognitive assessment of data collection instruments has been performed.

Practitioner and patient questionnaires to be utilized in this study have undergone an iterative process of pilot testing and refinement. This testing has allowed for prioritization of content, as well as ascertainment of question clarity, comprehension, and respondent burden. This pilot testing has taken place in dental offices and has involved Study Team practitioners and their patients.

The baseline questionnaires will be administered electronically with initial non-responders given the option to complete online or via telephone interview and the follow-up questionnaires will be administered via an online questionnaire with the initial non-responders followed up by telephone.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

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

8.1.1 *Unanticipated Problems*

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

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

8.1.2 *Serious Adverse Events*

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

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

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

8.2 Reporting Procedures

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

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

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

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

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

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

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

- US: 1-888-746-7231

- International: 919-595-6486

9 STUDY OVERSIGHT

In addition to the Grant PI's (GPI) and Study PI's (SPI) responsibility for oversight, external study oversight will be involve Medical Monitor Oversight Reporting. This oversight includes submission of a Medical Monitor Oversight Report (MMOR) to NIDCR at 6 month intervals, beginning approximately 6 months after enrollment begins until data collection is completed.

10 CLINICAL SITE MONITORING

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

Remote monitoring activities will primarily involve quality management (QM) procedures to ensure completeness and accuracy of data collection. These QM procedures are detailed in the protocol, Sections 13 and 15, as well as the study-specific Manual of Procedures (MOP). This study will follow the general guidelines for conducting monitoring for the network's observational clinical studies documented in Chapter 6 of the National Dental PBRN Manual of General Operations. Documentation of monitoring activities and findings will be provided to the practitioner, GPI, Study Principal Investigator, OCTOM, and the NIDCR. The NIDCR reserves the right to conduct independent audits as necessary.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Primary objective. Identify practitioner- and patient- based factors that contribute to practitioners' treatment decisions for patients with TMD pain.

This aim will evaluate potential associations between practitioner, practice and patient characteristics and dentists' treatment decisions. For each of the potential predictors, the null hypothesis is that there is no association between the potential predictor and each of the indicator variables representing treatment and decision outcome. The alternative hypothesis is that there is an association between the potential predictor and the outcome variable.

Secondary objective # 1. Identify the practitioner- and patient-based factors that contribute to the patient's adherence to treatment at follow-up.

The null hypothesis is that there is no association between practitioner, practice and patient characteristics and patient adherence to treatment. The alternative hypothesis is that at least some of these characteristics are associated with adherence to treatment.

Secondary objective # 2. Describe the observed changes from baseline in pain intensity and functional limitations over time.

The primary null hypothesis for this aim is that there is no difference in mean change in pain intensity and function from baseline to follow-up. The corresponding alternative hypotheses are that there are differences in mean change in pain intensity and functional limitations.

11.2 Sample Size Considerations

Study Design and Procedures

Dental Practitioners. Approximately 200 dentists will be recruited into the study, in order to achieve the goal of having at least 180 dentists who complete the study (i.e., 90% participation rate).

Patients. Each of the 180 dentists will be asked to recruit a target of 11 patients with a maximum of 20 patients for a total of 1980 patients. With a conservative estimated retention rate of 80%, our sample size at follow-up is $(1980 \times 0.8) = 1584$ patients in the study.

Sample size justification

- **Statistical method used to calculate the sample size**

Power estimation was based on logistic regression models for the primary objective and secondary objective # 1, and t test for secondary objective # 2.

Calculations were implemented using Power and Sample size software (<http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize>) to estimate the detectable alternative effects (Odds ratio).

- **Outcome measure used for calculations**

Binary outcomes were assumed for the sample size calculations, with the exception of that for the primary analysis for secondary objective # 2. The dependent variable for this objective is continuous, and was assumed to be normally-distributed.

- **Test statistic**

The test statistic for logistic regression analysis is the chi-square statistic. For the t test, the test statistic is the t statistic.

- **Null and alternate hypotheses**

Power and sample size calculations were based on the null and alternate hypotheses as stated in Section 11.1. Results of power calculations for logistic regression analyses are presented as the magnitude of odds ratios that would be detectable with at least 80% power, based on the proposed sample size and the assumed value of intraclass correlation coefficient (ICC).

- **Type I error rate**

Alpha was set at 0.05 for the sample size calculations.

- **Type II error rate**

Beta was set at 0.20 for the sample size calculations. In order to provide an additional level of conservatism regarding the sample size, as protection against errors in assumptions and possible additional comparisons, a power level of 80% was used in the calculations.

- **Method for adjusting calculations for planned interim analyses, if any**

No interim analysis is planned.

- **Assumptions used in calculations:**

- ***Assumed event rate for dichotomous outcome (or mean or variance of continuous outcome), justified and referenced by historical data as much as possible***

Power calculations for dichotomous outcomes were conducted for assumed event rates of 5, 10, 20, 30, 40 and 50%.

- ***Assumed dropout rates, withdrawal, missing data, etc., also justified***

A total loss to follow-up equal to 20% of the initial sample was assumed for the sample size calculations. This was based on experience from a previous cohort study where among 570 TMD participants at baseline, 480 (84%) completed the 18 month follow-up visit (Velly et al., Pain 2013; 152(10): 2377-83). The majority of the characteristics of those 90 subjects who dropped out are similar to those who remained in the study: 85% females (P = 0.59), the mean age = 36.02 years ± 12.66 (SD, P = 0.98), the mean catastrophizing was 1.31 ± 1.11 (SD, P = 0.55), the mean worst pain intensity = 7.36 ± 1.83 (P = 0.13) and 9% reported depression (n = 3, P = 0.81).

- ***Approach to handling withdrawals and protocol violations, i.e., to what extent data from withdrawn subjects will be evaluable, whether withdrawn subjects will be replaced.***

For patients who drop out or are lost to follow-up, all available data will be used in analyses for which they are appropriate. For instance, data for patients lost to follow-up will be included in analyses of baseline data.

If protocol violations occur, the specific scenario related to the violation will be reviewed in order to determine whether the resulting data is usable.

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

Calculations are presented for values of ICC ranging from 0.0 to 0.05, and for outcome prevalence ranging from 5% to 50%.

Discuss whether the sample size also provides sufficient power for addressing secondary objectives or for secondary analyses in key subgroup populations.

The proposed sample size provides substantial power to detect effect sizes representing relatively small departures from the null values. Secondary objectives were considered in the sample size calculations, and so will be adequately powered.

Sample size justification:

In order to account for the similarity among observations within the same cluster (dental practice), an effective sample size is estimated by dividing the total sample size by a variance inflation factor (VIF), equal to $1 + (m - 1)\rho$, where m is the number of observations per cluster and ρ is the intraclass correlation coefficient (ICC). Since there are no data to estimate the ICC, a possible range is shown below in Table 1 with the associated effective sample sizes.

Table 1. Effective number of patients per variance inflation factor (VIF)					
Clusters (k)	N/Cluster (m)	ICC	VIF	N	Effective N
180	8.8	0.00	1	1584	1584
180	8.8	0.01	1.078	1584	1469
180	8.8	0.02	1.156	1584	1370
180	8.8	0.03	1.234	1584	1284
180	8.8	0.04	1.312	1584	1207
180	8.8	0.05	1.39	1584	1140

Statistical plan and statistical power for primary objective and secondary objective # 1

Logistic regression modeling will be the primary statistical analysis for primary objective and secondary objective # 1. Analogous multivariable and mixed-model approaches will be used as appropriate to the specific analysis. We have demonstrated that the effective sample sizes described above (Table 1) will provide power of 80% to detect conservative odds ratios ranging from 1.14 to 1.85 for ICC values of 0.05 or lower as shown in Table 2. In these estimations, we considered the frequency of occurrence of outcomes for the primary objective and the secondary objective # 1 ranging from 5% to 50% and alpha equal to 5%.

Table 2. Odds ratios detectable by effective sample sizes						
Occurrence of outcome for primary objective and secondary objective #1	Effective sample sizes					
	1584	1469	1370	1284	1207	1140
	Intraclass correlation coefficient					
	0	0.01	0.02	0.03	0.04	0.05
Odds ratios detectable						
5%	1.71	1.74	1.77	1.8	1.83	1.85
10%	1.46	1.48	1.5	1.52	1.54	1.55
20%	1.30	1.31	1.32	1.33	1.34	1.35
30%	1.21	1.23	1.24	1.25	1.25	1.26
40%	1.17	1.18	1.19	1.19	1.20	1.21
50%	1.14	1.15	1.15	1.16	1.16	1.17

Statistical plan and statistical power for secondary objective # 2

The primary study outcomes for secondary objective # 2 are changes from baseline to follow-up with regards to TMD pain intensity (CPI= characteristic pain intensity: 0-10) and jaw function (JFLS-8 score; 0-10). CPI is the average of 0 to 10 ratings of “pain right now”, “average pain” and “worst pain”, multiplied by 10 to yield a 0-100 score. The power estimates for this aim, assessing a significant difference in the outcomes between treatment groups, show that the expected sample sizes would provide more than 80% power to detect conservative mean pain intensity difference of 20 points and jaw function difference of 2 between groups exposed and unexposed to different putative predictors (e.g. depression, sex, age) even when we consider large standard deviations [SD= 40 (CPI) and 5 (JFLS)] and ICC values of 0.05 or lower. In these estimations, we applied equal number of subjects to each treatment group.

11.3 Final Analysis Plan

Primary objective. Identify the practitioner and patient-based factors that contribute to practitioners' treatment decisions for patients with TMJD pain.

This aim will evaluate potential associations between practitioner, practice and patient characteristics and dentists' treatment decisions and implementation.

Treatments implemented by the practitioners will be tabulated, and percentages of patients who receive each treatment will be calculated. Potential predictors of each treatment choice will be evaluated individually, and variables found to have significant associations with the particular treatment will be used in the development of multivariable predictive models. Selection of variables for multivariable models will be conducted separately for practitioner/practice characteristics and for patient-based variables.

The primary statistical modeling approach will utilize mixed-model logistic regression analysis, which will account for multiple observations (patients) for each practitioner.

Separate prediction models will be developed for each of the defined treatment choices. Hypothesized predictor variables (predictors) will be evaluated in single-predictor regression models to evaluate their association with each of the treatment choices. The predictors will be included as fixed effects in the models. Multivariable models will be developed for defined blocks of predictors as follows: Network region will comprise a separate block; practitioner/practice-based variables; and patient-based variables. Predictors showing associations with treatments at $p < 0.20$ will be included in the block models. A liberal cutpoint for inclusion will be used in order to allow for individual variables to become more highly significant in multivariable models than in the single variable ones. Variables that are not significant in the block models will be removed from the model prior to constructing the final predictive model.

Following evaluation of the block models, a final predictive model will be constructed that will include variables that were retained in the respective block models. Goodness of fit of this model will be evaluated. Further development of the final model may include removal of non-significant predictors in order to improve the fit of the model to the data.

Secondary objective # 1. Identify the practitioner- and patient-based factors that contribute to the patient's adherence to treatment at follow-up.

The statistical analysis for this objective will follow the same approach as that for primary objective.

Potential predictors of treatment choices will be evaluated in separate analyses. Development of a predictive model will proceed as described previously, including possible further development of this model.

The primary statistical modeling approach will utilize mixed-model logistic regression analysis, accounting for multiple observations (patients) for each practitioner. A term representing the individual practitioner will be included in each model as a random effect, in order to appropriately incorporate correlation among the clustered observations.

Secondary objective # 2. Describe the observed changes from baseline in pain intensity and functional limitations for different treatments overtime.

The primary analysis for the secondary objective # 2 will compare changes in pain intensity and functional limitations from baseline to follow-up using mixed-model analysis of variance, accounting for the hierarchical structure of the data. Dependent variables for this analysis will include changes in pain intensity and functional limitations from baseline to follow-up.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

The following will be considered source documents.

Maintained by HP IDCC via electronic data management system:

- Doctor Patient Recruitment Log
- Patient Contact Form
- Patient Demographics Form
- Doctor Demographics Form
- Initial Patient Questionnaire
- Initial Doctor Questionnaire
- Patient One-Month Follow-up Questionnaire
- Patient Three-Month Follow-up Questionnaire
- Patient Six-Month Follow-up Questionnaire
- Doctor Follow-up Questionnaire
- Patient Withdrawal from Study
- Practitioner Withdrawal from Study

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

13 QUALITY CONTROL AND QUALITY ASSURANCE

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

The online questionnaires are built with data validation checks built in. If out of range values are entered by the patient or provider, the individual will be alerted and asked to provide a value that is in range. No single questions are required for completion of the online forms. Patients who move on to telephone follow-up will interact with a trained telephone interviewer from the CC. This interviewer will complete the interview, and questionnaire responses will be entered directly into the EDC system via the CC telephone interviewer interface. Data will be entered in real-time and will be subject to the same quality checks as the study participant interface. If a patient refuses to answer a question, this is noted by the interviewer in the online system. A subset of patient telephone interviews are monitored by CC supervisory staff. Although no interim analysis is planned, if interim data analysis is needed during the study period, the Data Manager will coordinate the activities with the Statistician. The datasets will be provided to the Statistician via secure data transfer method.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

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

14.2 Institutional Review Board

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

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

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

Approval (either centrally for those regions who agree to central approval, or regionally for those who do not) of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3 Informed Consent Process

Practitioners

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. RCs will execute consent procedures for practitioner study participants, based on regional IRB requirements, utilizing the general process described below for patients. Consent procedures will be administered prior to performing any study-related assessments or

procedures. Practitioners may withdraw consent at any time throughout the course of the study.

Patients

Participating practices will designate who will execute consent procedures for the study. In most cases this will be the participating dentist practitioner(s). Any personnel who will be assigned to obtain consent will be defined as study personnel and must complete required IRB training. Consent procedures will be administered in the participating practice prior to performing any study-related assessments or procedures.

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

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

Racial and ethnic minorities will be included in the study at least proportional to the composition in the dentist's TMD patient population. Individuals of any sex or racial/ethnic group may participate. Patients 18 years of age and older will be included in this study, except in Nebraska where consent is age \geq 19 years.

14.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study data will be released to any unauthorized third party without prior written approval of the sponsor.

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

15 DATA HANDLING AND RECORD KEEPING

Only study personnel (i.e., GPI, SPI, Co-Investigator's, study statistician, RCs, and CC personnel) and clinical site monitors will have access to the study data elements in the study database as described in Section 15.3 Types of Data. All study personnel will have completed the required training elements for human subjects research certification.

15.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the SPI. The CC will provide support and processes to allow for accuracy and completeness of data collected. All source documents must be reviewed by the CC staff, who will ensure that they are accurate and complete. Unanticipated problems must be reviewed by the SPI.

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

15.2 Data Capture Methods

Study-specific electronic questionnaires will be developed to include fields for all data elements required for participant assessments. The questionnaires are translated into a secure EDC system used to obtain data from practitioner and patient online baseline questionnaires as well as patient follow-up assessments and a practitioner follow-up assessment. An electronic (internet-based) data collection system will assist in ensuring that all required data are collected in the study database. As most fields will require a categorical response and some fields will ask for a numeric response, the data field in the database will be programmed to allow only certain values and ranges so that data entered into the electronic system can be validated and data errors be corrected. A similar database fully integrated into the online system will be used by CC telephone interviewers for those patients who undergo telephone follow-up and complete the surveys in that mode. For this situation, CC telephone interviewers will enter data into the electronic data management system and will respond to data queries generated by the EDC system. Reports and tools will be developed to help monitor the data activities.

Patients will be requested to submit the 1-, 3-, and 6-month follow-up assessments within the study assessment windows. Reminders and other tools will be used to encourage timely submission of these assessments; however, it is known that some patients may not comply. Follow-up assessments received outside of the study specified windows will be accepted; though this data may not be included in the analysis, it would still be of interest to the study team.

15.3 Types of Data

Responses from the patient data collection form will include demographic information, diagnosis of painful TMD and functional assessment, treatment adherence, treatment satisfaction, substance and alcohol use, overall health assessment, jaw functions, anxiety, depression, and oral habits.

Practitioner-level data will consist of demographic information from the National Dental PBRN enrollment questionnaire, as well as the following information from study questionnaires: Diagnosis of painful TMD, treatment recommendations, treatment adherence and unanticipated problems data.

15.4 Schedule and Content of Reports

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

The MMOR will be produced every six months after enrollment begins until data collection is completed. The purpose is to review cumulative enrollment data, participant safety and protocol adherence, and data integrity. The progress report will provide study site status, enrollment and retention status, status of outcome measures, major protocol changes since last reported, protocol deviations, unanticipated problems, quality management/monitoring and identified study challenges and solutions.

Reports to assess study retention will be produced every 2 weeks until data collection is complete and will be provided to the GPI, SPI, study team and NIDCR. These reports will provide ongoing monitoring of participant retention. Retention data will be closely monitored overall, by region, and by practice, and futility analyses will be performed as needed. For patients who are lost to follow-up, reports to assess reasons for loss will be produced after data have been obtained following the data collection period for each study follow-up assessment.

The procedure for locking the database prior to final analysis will be detailed in the study Data Management Plan developed by the Data Manager at the Health Partners IDCC. Briefly, the data will be locked and final datasets will be generated at the end of the study. Prior to locking the database, the HP IDCC Data Manager or designee will ensure all data is complete and clean and will obtain approval from the SPI to proceed with the data lock. The date and time of database lock will be documented.

15.5 Study Records Retention

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

As outlined by IRB regulations, data will be destroyed in an appropriate and safe way no sooner than three years from the date that the grant FFR is submitted to the NIH and with the GPI and SPI concurrence. The file connecting subjects' names with their unique identification number will be kept in a password-protected file by the CC and on the GPI's computer for a minimum of three years from the date that the grant FFR is submitted to the NIH and with the GPI and SPI concurrence before being securely erased, in accordance with IRB regulations.

15.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or GCP principles. The noncompliance may be on the part of the patient, practitioner, study team, or study staff. As a result of deviations, corrective actions may be developed by the study staff and should be implemented promptly.

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

Any protocol deviation that is reportable to an IRB must also be reported to NIDCR. NIDCR defers to the IRB for reporting time-frame requirements. Once a PD has been reported to an IRB, action must be taken to report the deviation to NIDCR. If the IRB overseeing the study protocol requires annual reporting of PDs to their IRB, that reporting frequency is acceptable to NIDCR.

16 PUBLICATION/DATA SHARING POLICY

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

17 LITERATURE REFERENCES

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SUPPLEMENTAL MATERIALS/APPENDICES

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

- APPENDIX A: Schedule of Events
- APPENDIX B: Subject Retention Plan

APPENDIX A: Schedule of Events

Procedures	Baseline	1-month follow-up +2 weeks	3-month follow-up + 2 weeks	6-month follow-up + 2 weeks
Assessment of Eligibility	X			
Administration of Consent	X			
Patient Contact Information (In Office)	X			
Patient Demographics (In Office)	X			
Baseline Questionnaire (Practitioner and Patient-confidential)	X			
Oral Exam*	X			
Treatment prescribed/administered by the practitioner (not a study directed procedure)	X			
Patient Follow-up Questionnaires (confidential)		X	X	X
Practitioner Follow-up Questionnaire				X

* Follow-up patient data collections will occur at 1, 3, and 6 months. This schedule may not necessarily coincide with the practitioner's clinical follow-ups as a part of treatment.

APPENDIX B: Patient retention plan

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

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

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

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

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

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

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

Methods to Minimize “Lost”

- 1) At subject enrollment, emphasize study requirements to subjects:
 - a. Study subjects are part of a longitudinal study (time in the study: 6 months), and the importance of follow-up questionnaires.
 - b. CC will contact subjects for completion of baseline questionnaire.
 - c. Entry criteria will include the ability and likelihood of maintaining participation throughout the study.
 - d. Collect information on:
 - i. Home telephone number
 - ii. Cell phone number
 - iii. Email address
 - iv. Contact information (including cellular telephone and/or email) of one person, and for whom they give permission for us to contact that will know of the subject’s whereabouts.

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

- 3) CC makes contact with study subjects prior to the follow-up assessment due dates.
- 4) Experience from the prior network has also shown that it is important to relieve burden on the practices. As such, the National Dental PBRN will request IRB approval for the CC to receive the subject contact information and the contact information of one person who does not live in the same household as the subject, to assist the CC in their follow-up with the study subjects post baseline.
- 5) The process for contacting non-responder practitioners for completion of the Initial Doctor Questionnaire and the Doctor Follow-up Questionnaire will be attempted by the RCs after the Study Manager informs RC which practitioners with whom to conduct reminders.
- 6) Number of Subjects per Practitioner Considerations:
Ask practitioners to enroll a target of approximately 11 patients with a maximum of 20 patients.
- 7) Given the above design features, subjects should not be “lost”. However, if a subject moves and contact is lost, the CC will implement tracking procedures.

Methods to Minimize “Missing Data”

- 1) Within the enrollment period, the office enrolls eligible subjects, with a target of approximately 11 patients with a maximum of 20 patients. Subjects will be required to complete their follow-up assessments at 1-, 3-, and 6-month post baseline visit.
- 2) Ask participating offices to develop a system to flag records of subjects in their practices who are participating as subjects in the study, as well as to flag study subjects in the office schedule. In this way, study personnel will be alerted to the fact that the subject is at the office. Flagging the subject in the schedule will help to ensure that subjects are not inadvertently scheduled when the practitioner will not be in the office.
- 3) Emphasize to practitioners as part of their initial study packages that the dentist has to be the motivational director of the study, especially regarding explaining to the study subjects that follow-up assessments are essential components of the study and make sure that the staff understands that the office is committed to taking the study on and seeing it through to completion.

Methods to Minimize “Refused”

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

Methods to Minimize “Unable”

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

Other Administrative and Design Methods to Increase Retention Rates

- 1) IRB/Informed Consent Considerations to Reduce Attrition
 - a. Incorporate permission into the ICF for all relevant study personnel to contact the subject. This will allow communications with the subject by study personnel without having to involve the dental office.
- 2) Financial, but non-coercive incentive to subjects to encourage continuing participation.

Additional Methods for Subjects Who Have Missed a Follow-up Assessment

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