Individualized Assessment and Treatment Program for TMD: Coping as a Mechanism

Clinical Protocol

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Principal Investigator: Mark D. Litt, PhD
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Grant Title: Individualized Assessment and Treatment Program for TMD: Coping as a Mechanism

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

INVESTIGATOR'S SIGNATURE

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 9/15/2022

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Individualized Assessment and Treatment Program for TMD: Coping as a Mechanism

Grant Number: 1 R01 DE028520

Study Description:

This is a proposal for an administrative supplement to the parent study, "Individualized Assessment and Treatment Program for TMD: Coping as a Mechanism" (U01 DE028520). The parent study is currently engaged in exploring the extent to which the training of coping skills per se is an important mechanism of psychosocial treatment. The current project seeks to lay the groundwork for expanding the range of treatment mechanisms examined to include therapeutic relationship factors (therapist support, empathy, acknowledgment).

Psychosocial treatments have been effective for temporomandibular disorders (TMD), but the mechanisms of action for these treatments are unclear. Most studies of psychosocial treatment, including the parent U01, have focused on relatively specific psychosocial mechanisms, including coping skills acquisition, pain management self-efficacy, decrease in catastrophizing, increased mindfulness, acceptance, and readiness to change behavior to ameliorate pain. The 2 therapist-delivered treatments in the parent study are packaged CBT or Individualized Assessment and Treatment (IATP). Left untested in this study are common therapeutic factors that often emerge as influential in pain outcome research. These common, non-specific therapeutic factors include (especially): the therapeutic alliance; interpretation and understanding; emotional expression; reinforcement; information; and reassurance and support. Because both conditions of the parent U01 involve similar levels of therapist involvement, therapist support and other treatment-non-specific variables cannot be tested clearly. One way to assess these factors is to introduce a pain treatment that *explicitly does not contain these factors*; i.e., a treatment that does not employ therapists or require supervision by health care professionals. There are currently no studies published in which therapist-led treatments have been compared to a mobile application-based treatment.

We therefore propose to pilot test a *mobile application treatment condition* (painTrainer©) added as an additional treatment condition to the parent study, and provided to 20 patients in the coming year. This condition will deliver the content of the CBT condition of the parent study, but will do so with no therapist contact. If this mobile application is found credible and acceptable it may be used in additional comparisons with treatments conducted by therapists. Thus at some point we will be able to parse the effects of cognitive-behavioral treatment content per se and therapist support factors. An

	additional benefit of testing such a mobile application is that it might in the future provide a means to expand the reach of pain management professionals to remote and underserved populations.	
Objectives*:	Primary Objective:	To test the feasibility, acceptability, and credibility of a mobile app treatment for chronic TMD/orofacial pain relative to treatment delivered by trained therapists.
	Secondary Objectives:	To examine preliminary differences in specific (e.g., coping strategies) and non-specific treatment effects (e.g., working alliance, perceived support-empathy), between the therapist-delivered treatments and the MobileApp treatment
	Tertiary/Exploratory Objectives:	The MobileApp condition will show some therapeutic effects on TMD/orofacial pain symptoms.
Endpoints*:	Primary Endpoints:	Treatment Feasibility Treatment Acceptability Treatment Credibility Treatment Adherence
	Secondary Endpoints:	Pain ratings
	Tertiary/Exploratory Endpoints:	Therapeutic alliance Parafunctional Habits Somatization Social Support Mood/Neuroticism Acceptance Stage of Change/Motivation
Study Sample:	20 men and women with a complaint of orofacial pain (> 3 on 0-10 scale for pain) of at least 3mo duration; minimum age 18 years; residing in greater Hartford, CT, area to permit frequent visits for treatment and follow-up. Those with pain of odontogenic or neuropathic origin, diagnosed with psychosis, taking narcotic pain medication, or those pregnant or intending to become pregnant will be excluded.	
Stage:	1	
Description of Sites/Facilities Enrolling Participants:	UConn Health is the state medical center for the State of Connecticut, USA. Patients will be seen exclusively at UConn Health, in the Dental Clinical Research Center, in Oral Radiology, and in therapy offices in the main hospital building.	

Description of Study Intervention/Experimental Manipulation:	painTRAINER (MobileApp condition) A 6-session web-based mobile pain management application comprised of 8 modules, dealing with cognitive-behavior strategies for managing chronic pain. Treatment is delivered virtually, with no live therapist presence.
Study Duration:	14 months
Participant Duration:	10-12 Weeks

1.2 SCHEMA

Design and Timeline of procedures

	Session/Time Point						
Treatment Condition	**Baseline** Wk -1, 0	Wk 1	Wk2	**Treatment** Wk 4	Wk 5	Wk 6	- Wk 6-7
	Screening **Pan X-Ray** **RDC Exam**						
painTRAINER	**Baseline Measures**						**Post-Tx Measures**
	Treatment Assignment **Impressions for split**	**Splint Delivered** **painTRAINER Patients Session 1**	**painTRAINER Patients Session 2**	**Splint Taper - night only** **painTRAINER Patients Session 4**	**Splint Discont'd** **painTRAINER Patients Session 5**	**painTRAINER Patients Session 6**	
	4 Times Daily Monitoring (14 Days)	**Start NSAIDs**	**Taper NSAIDs** **4 Times Daily Monitoring (7 days)**	**4 Times Daily Monitoring (7 days)**			**4 Times Daily Monitoring (7 days)**

1.3 SCHEDULE OF ACTIVITIES

TMD 3c: Schedule of Activities

Visit/session	Week	Participant Activity
1	-3 to -2	Potential Participant is initially screened for eligibility via telephone, or in person (e.g., in dental clinic)
2	-2	Diagnostic Evaluation (DE) visit (2 – 2.5 hours): · Orofacial Examination; Panoramic x-ray, impressions for splint taken · Administration of baseline measures (e.g., SCID, Orofacial pain and function) · Treatment Assignment · Introduction to Experience Sampling - Monitoring X 4 daily via smartphone (X 14 days; completed by treatment start)
3	1 – 3*	Splint is delivered NSAIDs started (e.g., naproxen 550mg po BID) Soft diet guidance given to patient painTRAINER website is loaded and bookmarked on patient smartphone Pt. completes tutorial and painTRAINER sessions 1 and 2 (TMD Online Session 1)
4	2 – 4*	painTRAINER session 3 (TMD Online Session 2) Start to taper NSAIDs Re-start Experience Sampling - Monitoring X 4 daily via smartphone X 7 days
5	3 – 5*	painTRAINER session 4 (TMD Online Session 3)
6	4 – 6*	Taper splint (e.g., wear as night guard only) painTRAINER session 5 (TMD Online Session 4) Re-start Experience Sampling - Monitoring X 4 daily via smartphone X 7 days
7	5 – 7*	Splint discontinued painTRAINER session 6(TMD Online Session 5)
8	6 – 10*	painTRAINER sessions 7 and 8 (TMD Online Session 6)
9	11-14 *	Administration of Posttreatment Self-Report Measures Re-start Experience Sampling - Monitoring X 4 daily via smartphone X 7 days

*Recognizing variability in schedules of working adults, flexibility is allowed in completion of study activities. Patients will have 10 weeks to complete the 6 treatment sessions. The Treatment and follow-up sessions will be conducted remotely.

2 INTRODUCTION

2.1 STUDY RATIONALE

Temporomandibular/orofacial pain disorders (TMD) are a group of painful conditions with multiple determinants. A number of psychosocial treatments for TMD have been developed, but overall effectiveness has been limited, and the mechanisms of treatment are unknown. Psychosocial treatments have been effective for temporomandibular disorders (TMD), but the mechanisms of action for these treatments are unclear.

Most studies of psychosocial treatment, including the parent U01, have focused on relatively specific psychosocial mechanisms, including coping skills acquisition, pain management self-efficacy, decrease in catastrophizing, increased mindfulness, acceptance, and readiness to change behavior to ameliorate pain. The 2 therapist-delivered treatments in the parent study are packaged CBT or Individualized Assessment and Treatment (IATP). Left untested in this study are common therapeutic factors that often emerge as influential in pain outcome research. These common, non-specific therapeutic factors include (especially): the therapeutic alliance; interpretation and understanding; emotional expression; reinforcement; information; and reassurance and support. Because both conditions of the parent U01 involve similar levels of therapist involvement, therapist support and other treatment-non-specific variables cannot be tested clearly. One way to assess these factors is to introduce a pain treatment that explicitly does not contain these factors; i.e., a treatment that does not employ therapists or require supervision by health care professionals. There are currently no studies published in which therapist-led treatments have been compared to a mobile application-based treatment.

We therefore propose to pilot test a mobile application treatment condition (painTrainer©) added as an additional treatment condition to the parent study, and provided to 20 patients in the coming year. This condition will deliver the content of the CBT condition of the parent study, but will do so with no therapist contact. If this mobile application is found credible and acceptable it may be used in additional comparisons with treatments conducted by therapists. Thus at some point we will be able to parse the effects of cognitive-behavioral treatment content per se and therapist support factors. An additional benefit of testing such a mobile application is that it might in the future provide a means to expand the reach of pain management professionals to remote and underserved populations.

It is expected that patients in painTRAINER mobile app condition will find the treatment acceptable and credible, and will derive some benefits in terms of reduced pain. Information gathered in this supplement will provide a platform for further exploration of the active cognitive, behavioral and therapist-related mechanisms of psychosocial treatment for TMD/orofacial pain. Such information will eventually allow us to test treatments that capitalize on both key interpersonal processes as well as cognitive and behavioral strategies that are most influential in managing this chronic pain. Additionally, however, if a credible and acceptable mobile app can approximate effects achieved with therapists, then access to pain management could be greatly extended to many patients we currently do not reach.

2.2 BACKGROUND

TMD/Orofacial pain from a biopsychosocial perspective. Studies of the symptoms, course, and treatment of TMD indicate that the disorder shares much in common with other chronic, ill-defined pain problems such as headache and back pain. The disorder appears to be multiply determined, with both psychosocial and physical factors playing a role in the development and maintenance of the disorder (Flor & Turk, 2011; Harper et al., 2016). Although persistent pain is the cardinal feature of TMD, stress, depression, disability and dysfunctional

illness are also significant aspects (Dworkin & Massoth, 1994). Also in common with headache and back pain is the finding that a variety of treatments have shown success with some patients. Among the more effective of these are cognitive-behavioral treatments (CBT) (Ehde et al., 2014; Gupta et al., 2019; Häggman-Henrikson et al., 2020; Randhawa et al., 2016). Despite much research, however, the mechanisms by which CBT works to ameliorate pain and distress are not clear.

Mechanisms of action of CBT. Cognitive-behavioral treatments (CBT) presumably improve pain by decreasing maladaptive behaviors and cognitions (in particular, catastrophizing) that exacerbate pain, and by increasing adaptive cognitions and coping (Turk et al., 1983; Turner & Romano, 2001). These changes should in turn lead to improvements is confidence (self-efficacy) for pain management (Jensen et al., 1991) and improvements in momentary and durable mood states (Litt et al., 2009; Litt et al., 2010). This is a compelling model. However, relatively little research has been conducted to determine if cognitive-behavioral treatments actually lead to these kinds of changes, and if so, whether those changes are accounting for symptom reduction (Burns et al., 2020). What research has been done has not shown consistent mechanism effects for the acquisition of pain coping skills (Aggarwal et al., 2010). The evidence does suggest outcomes might be improved if coping skills were trained in a more effective manner, and tailored to individual strengths and weaknesses. What is less clear is whether even adaptive changes in cognitions, affects, and behavior can account for all of the treatment effects seen in CBT-oriented interventions.

Other potential mechanisms: Common factors and common therapist factors. Somewhat contrary to the idea that specific aspects of treatment (e.g., coping skills training; cognitive control) are responsible for adaptive change in pain, the common factors model suggests that factors common to all treatments are responsible for producing treatment-related changes (Burns, 2016). Five classes of common factors are usually identified: change processes (e.g., expectancies), therapist qualities (perceived competence), relationship elements (therapist alliance, empathy, support), treatment structures (e.g., predictability), and client characteristics (Cosio, 2016). Outside of client factors (e.g., sex, motivation), the greatest source of common variance are therapist factors, accounting for perhaps 30% of treatment effects (Hubble et al., 1999). These common therapist factors include: (especially) the therapeutic alliance; interpretation and understanding; emotional expression; reinforcement; information; and reassurance and support (Garfield, 1995; Imel & Wampold, 2008). Although the common therapist factors are undoubtedly important, it is not clear how they translate into initial or prolonged behavior change or adaptation. Presumably, support and reinforcement for adaptive behavior when in company with others will improve mood and increase self-efficacy for coping and pain management. The influence of common, or therapist, factors is difficult to determine from most trials, however, because almost all treatments in these trials are delivered by therapists. Thus, therapist factors are difficult to disentangle from other active mechanisms. To assess the influence of therapist factors, treatment would have to be provided that was identical in content, but that did not involve interaction with a therapist.

The Parent Study: TMD3c U01DE028520. The parent study, “Individualized Assessment and Treatment Program for TMD: Coping as a Mechanism” (U01 DE028520), is currently engaged in exploring the extent to which coping skills, if tailored to the patient, can effect improvements in chronic pain and functioning. This is considered a significant test of the social learning model of pain management. To do this, a highly individualized coping skills treatment was devised that is based on patients’ own reports of their pain and coping in near real-time. This treatment, *Individualized Assessment and Treatment (IATP)* is being tested against a more conventional, or *packaged, cognitive-behavioral treatment program (CBT)* that covers typical topics for behavioral pain management in a fixed format. The present Supplement application. The current supplement application seeks to expand the range of treatment mechanisms examined to include therapeutic relationship factors (therapist support, empathy, respect, acknowledgment). Despite the strengths of the parent study, the design is not optimal to detect the influence of therapist factors on pain outcomes. Because both conditions of the parent

U01 involve similar levels of therapist involvement, therapist support variables cannot be tested clearly. The addition of a pilot study of a mobile application is both timely and needed. Although numerous mobile applications are available for the monitoring and management of chronic pain, almost none have been systematically studied for efficacy or for active elements, and none have been studied by themselves alongside treatments delivered by therapists (Martin et al., 2021). Mobile applications do, however, have promise to deliver some pain reduction (Irvine et al., 2015), as well as amelioration of anxiety (Bhatia et al., 2021), to a widespread population without the need for medical or therapist supervision. If successful, these can greatly improve access to care.

Significance

The addition of a treatment condition delivered without therapists will enhance our understanding of the mechanisms of action of psychosocial treatments for multiply determined pain disorders such as TMD. This project will offer an opportunity to pilot test a mobile program for TMD pain in controlled circumstances, against treatments delivered by trained personnel. If a credible and acceptable mobile application is demonstrated with these pilot patients it would provide a basis for a full-scale trial. Eventually we hope to determine the importance of specific content and skills, above and beyond the influence of common therapist effects. In addition, however, this pilot supplement would also provide support for further study of programs that would extend the reach of care for patients with chronic pain who may not be able to attend supervised treatment with health care providers.

2.3.1 KNOWN POTENTIAL RISKS

There are no serious risks associated with participation in this research. Minor risks are as follows:

1. Clinical Deterioration. As with any treatment for a medical issue, participants could experience clinical deterioration (worsening of pain or other life issue) during the course of the study, especially if the treatment to which one is assigned is not effective in any specific case.

2. Panoramic X-Ray. In order to rule out jaw disorders, participants will undergo a panoramic x-ray, which exposes participants to radiation.

3. Discomfort with Splint. All participants will be fitted with a splint, or mouth guard, placed on the upper teeth. Some people may find this uncomfortable, especially at first.

4. Confidentiality/Risk of unauthorized disclosure of confidential material. Another potential risk is a possible breach of confidentiality.

5. Risk of gastrointestinal upset secondary to taking NSAIDs (naproxen sodium 550 mg po BID; or 400 mg Ibuprofen BID or TID X 14 days). Use of NSAIDs like those proposed for this study carry a small (less than 10%) risk of causing GI distress. This medication is also contraindicated for those with kidney disease. Subjects with known sensitivity to NSAIDs, those with documented kidney disease, or those who experience GI upset during the course of the study may be placed on acetaminophen as an analgesic, in consultation with the patient's physician.

2.3.2 KNOWN POTENTIAL BENEFITS

All subjects will receive free treatment, free radiographs, and free medication. During treatment we will be aware of any clinical deterioration that may occur and will be able to refer participants for additional treatment if they request or need it. This is a greater level of clinical surveillance than is available in usual treatment. Our experience suggests, however, that many subjects will respond well to the treatment program, and to the self-monitoring program, and will perceive the project as helping them to reduce their TMD pain. We believe that the small potential risks are outweighed by the potential benefits of treatment and self-monitoring that may accrue to participants in the study.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

- *Rationale for the necessity of exposing participants to risks*:

TMD/Orofacial pain problems are widespread. This research has potential to deliver a new, more effective treatment, and to expose important mechanisms that can be used in treatments for others. The small potential risks are outweighed by the potential benefits of treatment and self-monitoring that may accrue to participants in the study. There may also be long-range benefits for improved treatment of TMD for others as a result of this study. Results may also be applicable to other, similar, pain problems.

- *A summary of the ways that risks to participants were minimized in the study design:*
  1. Clinical Deterioration. The research staff will monitor participants in for signs of deterioration, and will refer participants for more intensive treatment if such a problem arises. If participants pursue treatment outside the study, they will be responsible for the costs of that treatment.

  2. Panoramic X-Ray. The estimated radiation exposure received by each participant for the panoramic view is 1.5 millirem (15 uSv). This dose equivalent would be less than that received by an individual flying from New York City to San Francisco.

  3. Discomfort with Splint. All participants will be fitted with a splint, or mouth guard, placed on the upper teeth. Participants will be instructed that they may stop using the splint at any time. Some people may find the splint uncomfortable at first. If discomfort occurs, participants will be instructed to contact the study dental assistant or research assistant, so that study staff can arrange for a prompt visit (within a couple of days) to make adjustments to the splint. If the discomfort continues, participants may discontinue using the splint

  4. Confidentiality/Risk of unauthorized disclosure of confidential material. Study staff will make every effort to maintain participants' confidentiality. Research records will be labeled with a code number, which will be determined using a random numbers list. A master list that links participants' names with their code number will be maintained in a separate and secure location. Consent forms in electronic form will be stored in a secured location (a secure server) apart from the research record. Participants' names will not appear in any publication. Only research staff associated with this study will have access to the research record, or to the master list linking participants' names with code numbers. If participants' information is used in future research, all identifiers, such as name and date of birth, will be removed. After removal of names and other identifiers, the information participants provide could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from participants.

5. Risk of gastrointestinal upset secondary to taking NSAIDs (naproxen sodium 550 mg po BID; or 400-600 mg Ibuprofen BID or TID X 14 days). Participants with known sensitivity to NSAIDs, those with documented kidney disease, or those who experience GI upset during the course of the study may be placed on acetaminophen as an analgesic, in consultation with the patient's physician.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
To test the feasibility and acceptability of a mobile app treatment for chronic TMD/orofacial pain	1. Patient acceptance of assignment to treatment 2. Scores on Treatment Acceptability scale 3. Scores on Treatment Credibility scale 4. Patient adherence to treatment assignments	This is a feasibility study. The primary endpoints are thus treatment acceptability, credibility and feasibility of the procedures.	A mobile app for pain management should deliver the didactic content of a CBT program, and will also prompt patient to monitor their own progress, without having to travel or make time to see a therapist.
Secondary			
To determine if patients given this treatment record reduced pain and interference with lifestyle	1. Graded chronic pain score 2. Jaw Functional Limitation Scale-Short form (JFLS) 3. MPI - Interference 4. CES-D 5. STAI-Trait 6. Pt Global Impression of Change	Although power will not be sufficient to determine if this treatment is efficacious, we do expect some improvement in symptoms.	painTRAINER is designed to provide skills that patients can use to manage their pain. The program allows them to monitor their progress and adjust their behavior as necessary. These activities should result in reduced pain and improved functioning
Tertiary/Exploratory			
None			

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a one-group feasibility trial in which patients presenting with TMD pain are assigned to the painTRAINER program. All participants will receive standard TMD, physician-guided treatment, including fitting for splints and NSAIDS recommendations, if appropriate. Participants will be followed during treatment and at posttreatment to monitor fluctuations in pain and coping over time, and to help insure that participants remain engaged.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This design was chosen to test the study hypotheses for a feasibility trial:
(1) The mobile application (painTrainer) will prove to be a feasible and acceptable intervention, as evidenced by the requisite number of patients being recruited in a reasonable time span, and agreeing to treatment using the application.
(2a) The mobile application (painTrainer) will prove to be a credible treatment, as evidenced by scores on a measure of treatment credibility (the treatment credibility/expectancy questionnaire), as compared against published credibility scores.
(2b) The mobile application (painTrainer) will prove to be as credible as the therapist-led treatments currently provided in the Parent study, as demonstrated by tests of non-inferiority on credibility scores.
(3) Patients in the MobileApp will show acceptable adherence to the scheduled procedures, as evidenced by scores on a treatment adherence measure, and through completion of exercises monitored by the painTRAINER mobile app (i.e., > 80% completion of recommended exercises).

4.3 JUSTIFICATION FOR INTERVENTION

This intervention will allow a test of delivery of skills content without the influence of therapist effects. The study will thus pave the way for an investigation of the role of therapist effects per se on behavioral pain management approaches.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit (posttreatment visit) as shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY SAMPLE

5.1 INCLUSION CRITERIA

Inclusion criteria are as follows:

- Age at least 18 years
- Complaint of either bilateral or unilateral pain, scoring > 3 on a 11-point pain scale (scored from 0 to 10), in the area of the temporomandibular joint
- Pain has persisted for a period of at least 3 months by patient self-report. Pain may be constant or intermittent.

5.2 EXCLUSION CRITERIA

Exclusion criteria:

- Contraindications to TMD treatment (as determined by the consulting oral surgeon)
- Inadequate fluency in English
- History of prior surgery for TMD
- Receiving concurrent treatment for orofacial pain (including orthodontic or physical therapy)
- Have a condition that requires the use of an oral appliance (e.g., sleep apnea)
- Diagnosed as having pain of neuropathic or odontogenic origin
- History of rheumatoid disease or autoimmune disease (e.g., rheumatoid arthritis; lupus) currently being treated with anti-inflammatory drugs
- History of kidney disease or current kidney issues
- Extensive anatomical destruction or deterioration of the TM joint
- Current treatment of chronic pain issue with anti-inflammatories (e.g., Indomethacin; methotrexate; dexamethasone) or opioid analgesics
- Carrying a diagnosis of psychosis[a] (as per self-report on Quick Screen)
- Pregnant or anticipating pregnancy (due to prescription of NSAIDs)

[a]Among persons carrying a diagnosis of psychosis it may be difficult to parse symptoms attributable to the psychosis from those attributable to pain. In addition, those with psychosis tend to report less pain than non-psychotic persons (Singh et al., 2006). Thus those with psychosis will be excluded

5.3 LIFESTYLE CONSIDERATIONS

During treatment all patients will be advised to:

1. Alter their diets to avoid chewy foods or those difficult to chew, and to choose soft foods
2. Wear the intraoral splint full time if possible x 4 weeks, and then only at night for 2 weeks thereafter, or as patient chooses at that point. This schedule is just suggested, and patients may use the splint as they wish. We will record hours of splint use per day.

These lifestyle alterations are considered “homework,” and will be monitored for adherence weekly. Patients who do not adhere to these recommendations will not be dropped from the study. Adherence to medication, diet and splint use will be used as covariates in analyses of outcomes.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for

participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include a change in plans to become pregnant during the course of the study or lifting of physical activity restrictions previously in place. Rescreened participants will be assigned the same participant number as determined in their initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment and Retention Procedures

Recruitment and screening. Patients will be recruited both through the University dental clinics and through newspaper, radio and internet advertisements. Persons will respond to the advertisement by telephone. Those who call will be told that the purpose of the project is to test different TMD treatments. Those interested will be screened over the telephone for basic inclusion/exclusion criteria. Those who meet eligibility at this point will be scheduled within 14 days for a diagnostic evaluation (DE). A remote consent process will then be conducted over the phone, with documentation of consent enabled via REDCap.

Consent Process. Those persons who appear to be eligible on the Quick Screen will be e-mailed a link to a REDcap version of the informed consent form prior to any assessment. The REDCap system can be accessed using a smart phone, computer, laptop, or tablet device. REDCap (Research Electronic Data Capture) is a secure, HIPAA-compliant, web-based application. An electronic file that links patient name and number will be maintained and managed using REDCap electronic data capture tools hosted at UConn Health. A research assistant will schedule a time with the participant to review the consent form on the telephone as the participant reads it to assure comprehension. The REDcap form will allow addition of an e-signature on the part of the participant, as well as a signature from the research assistant who administered the consent. Those who request being allowed to read and sign the consent form in person will be scheduled for an appointment at UConn Health solely for the consent process. Persons meeting initial eligibility criteria and consented will be scheduled for a baseline diagnostic evaluation session (DE)

Baseline session - DE. The DE will consist of questionnaires administered to the participant by research assistants (RAs), as well as a clinical evaluation of the orofacial pain problem conducted in the dental clinic by study clinical staff (i.e., the participating dentists). Questionnaires will be administered via REDCap, with assistance by an RA provided over the telephone if necessary.

The clinical examination will be conducted in the dental clinic of the Dental Clinical Research Center of UConn Health. At this session potential subjects will be examined by the participating dentist(s) who will rule out neuropathic or odontogenic pain and diagnose the type of orofacial pain according to the Diagnostic Criteria for TMD (DC/TMD). Following this examination prospective subjects will have a panoramic X-ray taken to rule out gross arthritic or anatomic damage to the TM joint. For those meeting criteria by the DC/TMD impressions will be taken for an acrylic, flat-plane disoccluding splint. Subjects will be given $40 for completion of baseline measures. All subject incentives will be delivered via check or via E-gift card e-mailed to the participant, if possible.

Posttreatment Data Collection. At the 6 weeks point (or after 6 sessions have been completed) patients will be asked to complete follow-versions of the dependent measures. At this point, subjects will once again be asked to participate in ES via smartphone app for 7 days to determine if situation-specific coping has changed in treatment. $25 will be offered for Posttreatment data collection + up to $40 for ES for 1 Week. Subject incentives will be delivered via check or via E-gift card e-mailed to the participant, if possible.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

MEASURES & INSTRUMENTS (SEE TABLE 1)

TMD Diagnostic Protocol: Screening and Classification (SCID & DC/TMD Axes I and II)

Initial screening of potential subjects will be conducted over the telephone using an inclusion/exclusion criteria checklist administered by a research associate. Potential participants will receive e-mail links to complete questionnaires via REDCap. Screening questionnaires administered remotely will include the psychotic screening portion of the Structured Clinical Interview for DSM-V (SCID-V; First et al., 2015), plus the DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure—Adult (Association, 2013), which can screen for a variety of psychiatric issues, including depression, suicidal ideation, anxiety, and sleep disturbances, among others. Classification of TMD subjects' orofacial pain problem will be done using the revised Diagnostic Criteria for Temporomandibular Disorders History Questionnaires (Ohrbach R. (Editor), Version 15May2016; Schiffman et al., 2014). The DC/TMD procedures are an update of procedures laid out by Dworkin & LeResche (1992), with increased sensitivity and reliability of diagnoses, particularly in Axis I. The examination will be conducted by our oral surgeon and orofacial pain specialist investigators, who have experience with the DC/TMD examination. Prior to patient recruitment the examiners will train on sample cases using the DC/TMD procedures manual until they attain 90% interrater agreement on specific Axis I diagnoses. During the recruitment phase the examiners will test on each 20th case to maintain reliability. DC/TMD Axis II assessment will be conducted using the following, as per the assessment manual, and administered remotely via REDCap: The Jaw Function Limitation Scale (JFLS-20; Ohrbach, Granger, et al., 2008); The Patient Health Questionnaire (PHQ-15; Kroenke et al., 2002); The General Anxiety Disorders scale (GAD-7; Spitzer et al., 2006); and the Oral Behaviors Checklist (Ohrbach, Markiewicz, et al., 2008). In addition to the above, we will also collect information on any use of concomitant medications, at intake and at each follow-up, as well as non-protocol concomitant treatments for orofacial pain patients may have sought. See Table 3 for schedule of instrument administration.

Dependent Variables (IMMPACT recommendations)

Primary Dependent Variables. The same battery of dependent measures used in the Parent study will be administered to the MobileApp patients recruited for this Supplement. However, due to the preliminary nature of this study, the primary dependent variables will be those tied to feasibility and acceptability. Patients in this study will be administered the Treatment Acceptability and Adherence Scale (TAAS) (Milosevic et al., 2015) to assess treatment acceptability. The TAAS is in widespread used. Credibility of the treatments will be assessed using the Credibility/Expectancy questionnaire (CEQ) by Devilly & Borkovec (2000). The CEQ is the most widely used measure of treatment credibility and expectancy in psychotherapy research (Thompson-Hollands et al., 2014). These two measures will serve as outcomes relevant for the MobileApp condition

Supplemental Dependent Variables. The supplemental dependent variables in this study will be Pain Intensity, Depression and Interference. A number of secondary outcomes will also be assessed and analyzed as per guidelines from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT; Haythornthwaite, 2010; Turk et al., 2003). All outcomes will be evaluated on day of recruitment (baseline) and again at the posttreatment point. The six outcome domains are: (1) pain (including intensity and pain experience); (2) physical functioning; (3) emotional functioning; (4) participant ratings of improvement and satisfaction with treatment; (5) symptoms and adverse events; and (6) participant disposition (e.g. adherence to

treatment, reasons for premature withdrawal). Specific instruments were chosen on the basis of recommendations by Haythornthwaite et al. (2010). Several instruments were included because they have proven useful in our previous studies, and may form a basis for comparison. All instruments chosen have demonstrated acceptable psychometric characteristics.

An additional process measure, the debriefing questionnaire, will be administered at posttreatment to help us determine whether the painTRAINER treatment program efficacy might be enhanced with the addition of some therapist or counselor interaction.

Table 1. TMD 3c: Schedule of Instruments and Follow-ups for all conditions;
Supplement MobileApp condition (Pre-post Only) |----------|

Instrument	Intake[a]	6 wks[b] (Post-Tx)
SCREENING & Dx Eval VARIABLES		
Quick Screen, Demographics	X	
Slosson Oral Reading Test (if indicated)	X	
SCID V: Psychotic Screen	X	
DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure	X	
*DC-TMD Examination With Panoramic X-Ray	X	
DC-TMD Pain locations drawing	X	
Jaw Functional Limitation Scale-long form (JFLS)	X	
Generalized Anxiety Disorder-7 (GAD-7)	X	
Physical symptoms Patient Health Questionnaire-9 (PHQ-9)	X	
Physical symptoms Patient Health Questionnaire-15 (PHQ-15)	X	
Parafunctional Oral Behaviors Checklist (OBC)	X	
Concomitant Medications & Concomitant Non-Protocol Treatments	X	X
Client locator form	X	
DEPENDENT MEASURES	X	
Graded Chronic Pain Scale	X	X
Jaw Functional Limitation Scale-Short form (JFLS)	X	X
MPI - Interference	X	X
CES-D	X	X
STAI-Trait	X	X
Pt Global Impression of Change		X
PROCESS VARIABLES		
Brief Pain Coping Inventory	X	X
Pain Catastrophizing Scale	X	X
Chronic Pain Acceptance Questionnaire	X	X
Facial Pain Self-Efficacy Scale	X	X
MPI – Spouse support	X	X
PHQ15 somatization	X	X
NEO neuroticism	X	
Pain Stages of Change Quest	X	X
Working Alliance Inventory (WAI-C-Short Form)[c,d]	X	
Posttreatment Debriefing		X
TREATMENT ACCEPTABILITY & CREDIBILITY		
Treatment Acceptability and Adherence Scale	X	X
Credibility/Expectancy Questionnaire	X	X
Experience Sampling Measures‡	X	X

[a]Intake and DE measures will be administered via tele- or video conference, and recorded in REDCap, except for DC-TMD exam, which will be conducted in person.
[b]Follow-up surveys and questionnaires will be administered via tele- or video-conference
[c]The WAI will be administered to participants after the 2nd scheduled treatment session.
[d]Added to the WAI will be 3 Empathy Questions from the MOPQ Common Factors Questionnaire (Finsrud et al., 2022).
‡Experience Sampling (ES) via smartphone app Process measures will be taken 4 times per day for 2 wks, between Intake & treatment start (Weeks -2 to 0), and for 1 week at **Wks 2 and 4 (during treatment), and at week 6 (postTx).**
ES measures will include the following:

- **Pain (left & Right) (0 – 5)**
- **Pain control (0 – 5)**
- **Catastrophizing (0 – 5)**
- **Somatizing (0 – 5)**
- **Mood state** (8 items, each scored 0-5, grouped as High Affect – High Arousal, High Affect – Low Arousal; Low Affect – High Arousal; Low Affect – Low Arousal)
- **Situation (selection of 5 situations)**

Coping Responses (selection of 11 possible; e.g., using relaxation; using medication)

Pain intensity at each assessment point will be calculated as Characteristic Pain Intensity by averaging ratings of current pain, average pain, and worst pain in the past week from the Graded Chronic Pain Scale (GCPS; Von Korff et al., 1992); a reliable retrospective measure (Stone et al., 1997). Each item is scored from 0 -10. Other dimensions of pain per se, (sensory and affective dimensions), will be assessed using the short form of the McGill Pain Questionnaire (MPQ-SF; Melzack, 1987).

Physical functioning. General interference with activities will be measured using the interference scale from the Multidimensional Pain Inventory (MPI; Kerns et al., 1985). The MPI also contains questions about sleep, which is often affected in pain patients. Jaw function will be assessed using the Jaw Functional Limitation Scale (JFLS; Ohrbach et al., 2008). The JFLS is a 20-item questionnaire that assesses mastication, jaw mobility, and verbal and emotional communication.

Emotional functioning. Depression symptoms will be measured using the using the 20-item Center for Epidemiological Studies Depression scale Revised (CESD-R; Eaton et al., 2004), a useful measure of distress in medical populations. In addition we will measure anxiety mood using the Trait version of the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). Participant rating of improvement will be assessed with the Patient Global Impression of Change scale (PGIC; Hurst & Bolton, 2004). The PGIC consists of two questions in two different formats asking for a global assessment of "change if any, in activity limitations, symptoms, emotions and overall quality of life." A 2-point change on the rating scale has been calculated to be clinically significant.

Symptoms and adverse events will be collected weekly during treatment and at each follow-up by research assistants. Procedures are described in the Human Subjects section. Participant disposition, including retention in treatment and follow-ups, and reasons for withdrawing, will be collected in a patient tracking database.

Dispositional Variables-Moderators/Mediators

The Parent study contains measures of dispositional moderators based on past research. These include measures of Coping, Catastrophizing, Acceptance, Somatization, Neuroticism, Readiness to change, and Self-efficacy. General coping will be assessed with the Brief Pain Coping Inventory (BCPI; McCracken et al., 2005). Common factors: As has been suggested here, the effectiveness of therapy is may be significantly attributable to the therapeutic relationship. We are already administering the Working Alliance Inventory (Short Form) (WAI; Horvath & Greenberg, 1986) to assess therapeutic alliance. To this we will add 3 items specifically tapping therapist empathy, from the MOPQ Common Factors Questionnaire (Finsrud et al., 2022). Although the MobileApp patients will not have a therapist to rate, the questions will be altered to refer to "Treatment Staff."

Experience Sampling (ES) of pain, coping, and affects via Smartphone app

As in the treatment conditions currently being run in the Parent study, patients in the MobileApp condition will also engage in Experience Sampling of pain, affect, cognitions and coping behaviors, so that this aspect of treatment will be equivalent across conditions. The MobileApp patients will be monitored using the same MetricWire application as the rest of the patients. Just as in the STD+CBT condition, those in the MobileApp condition will be asked to make momentary recordings, but those recordings will not be used to influence treatment. This recording approach was designed to not be reactive, by tapping multiple events and not allowing reviews of recording (Barta et al., 2011).

During an initial training session participants will be instructed to answer each question with as little reflection as possible. Participants will be asked to carry their phone at all times between 8AM and 10PM in Weeks -1 and 0 (after baseline interviews, but before treatment starts), for 7 days during weeks 2 & 4 while in treatment, and again for 7 days after completion of treatment, and later during the follow-up (See above: **Schedule of Activities**). The smartphone-based ES system will administer surveys and record responses. The system will be

programmed to prompt subjects on a quasi-random basis 4 times per day, with one randomly scheduled prompt in each of four 210-minute time periods from 8:00AM to 10:00PM (adjustable for different schedules). This frequency of recording was chosen to enable us to capture as many moments in a patient's day as possible without being disruptive (Litt et al., 2004; Litt et al., 2010). Subjects will have the option of delaying responding to a prompt for 5, 10 or 15 minutes if recording is inconvenient. Delays longer than 15 minutes will be classified as missing.

As in the parent study, participants will earn $5.00/day for every day of satisfactory experience sampling recording (i.e., $\geq$ 3 recordings per day). A bonus of $5.00 will be paid in a week in which $\geq$ 3 recordings were made every day, for a possible total of $40.00 for that week.

ES Recording format. Participants will respond to survey questions on the phone screen. For every recording the subject is directed to record perceptions along a 6-point "slide-scale" ranging from "0=Not at all" to "5=Very much." Responses are time-and-date-stamped, and entry of out-of-range data is not possible. If data entry is abandoned in the midst of an assessment, the system will prompt the participant again and resume the assessment. Assessment data will be electronically stored in spreadsheet format on a system server maintained by the system contractor, backed up nightly, and accessible to our study team in real time. Data from each participant engaged in ES monitoring will be examined periodically for missing responses by a research assistant. If a participant misses two recordings in a row, the research assistant will contact the individual by phone or text.

ES data. Patients will respond during ES to items related to pain intensity (right and left sides of the face) and unpleasantness experienced (right and left sides), and two items related to perceived control over pain ("am able to decrease pain;" "am able to control pain"). Self-efficacy will be measured with: "How confident are you that you can cope with your current pain?" Catastrophization will be assessed using two items borrowed and modified from the Coping Strategies Questionnaire (CSQ; Rosenstiel & Keefe, 1983) catastrophization subscale, are "Worried about Pain" and "Pain is Terrible," (α = .87). Somaticizing will be measured using 2 items reflecting the tendency to process stress in terms of physical symptoms: "Concerned that jaw will start hurting," "Paying attention to my jaw pain." Current mood state will be recorded using 8 items derived from a semantic space analysis of adjectives in the circumplex model of affective experience (Larsen & Diener, 1992; Russell, 1980). The items are combined to yield four reliable mood composites based on dimensions of pleasantness and arousal. Situations will be assessed using categories (Home, With others, etc.), as well as with free voice response. Coping responses will be recorded by asking the subject what if anything he or she had done to help manage any pain he/she might have experienced in the last 10 minutes. The 11 coping response items were derived from inventories assessing coping in pain patients (e.g., the CSQ), and from surveys of patients in TMD pain treatment, and grouped into 4 subscales: active-behavioral (e.g., "I used ice or heat," "Relaxed"); active-cognitive (e.g., "I thought pleasant thoughts"); resignation ("I just accepted the pain"); and distraction ("I distracted myself," "I looked for support from someone"). One item will also record if "Nothing" was done to deal with pain. Internal consistency reliabilities of the coping subscales exceeded α=.65 in past studies. Two items will be added reflecting Acceptance-based strategies (as opposed to pain control–related strategies; Hayes et al., 1999) based on Vowles et al.(Vowles et al., 2007): "Tried to accept the pain and focus on what I was doing; "Told, myself that the pain does not have to stop me." An additional item reflects "guarding," which is characteristic of somatizing, "Restrict my activity to keep from hurting myself." Patients will also be asked to record an answer using free response (voice recording), to be categorized by the RA staff later. This will allow us to compare free responses with categorized ones. Effectiveness of the coping response will also be assessed.

Treatment: STD+MobileApp condition (i.e., painTRAINER©)

The MobileApp condition participants will engage in standard (STD) conservative dental treatment for their TMD pain (i.e., placement of maxillary splint; prescription of NSAIDS; prescription of soft diet; see below re Concomitant Treatments). However, instead of a therapist-led psychosocial component, the STD+MobileApp condition will employ an *online cognitive-behavioral treatment program* known as painTRAINER. The painTRAINER program is an interactive, online tool that teaches strategies that patients can use to manage pain. The program was developed by experienced pain clinicians and researchers, led by Christine Rini at Northwestern, and Frank Keefe at Duke (R01AR057346), and refined by researchers at University of Melbourne. This program was chosen 1) because of its close correspondence to the content and session time provided in the STD+CBT condition; and 2) because of its current use in research, demonstrating effects on depressive symptoms, catastrophizing, and pain interference (Allen et al., 2021). PainTRAINER is also currently being used by the Pain Management Effectiveness Research Network (Lyn DeBar, PI: UH3AG067493). The painTRAINER program is made up of 8 sessions, each lasting about 45-60 minutes. It was designed so that registered researchers are able to access the data collected (e.g., session completion data) allowing tracking of adherence. Workbooks and scripts for RAs are also provided. For the purposes of this trial, the first 2 and the last 2 components of the painTRAINER program will be combined, creating 6 weekly sessions of about 50-75 minutes each, as in the two treatment conditions currently being run in the Parent Study. An outline of the sessions for MobileApp treatment is in Table 2. Because painTRAINER is a general program for chronic pain, some modifications will be made to the overall patient program (though not to the painTRAINER program itself) to make it more similar to the TMD-specific CBT program in the IATP+CBT condition. Specifically, in addition to attending to Session 2 painTRAINER content, patients will be instructed to read prepared materials on managing parafunctional habits, and view a video on masseter massage. These will be the same written materials and video that are recommended for patients in the two therapist-led conditions. Patients in the MobileApp condition will be asked to complete the same worksheet and homework assignments as those in the therapist-led conditions.

Table 2. Session Outline for painTRAINER MobileApp treatment condition

Session 1	1. Understanding pain and relaxation 2. Brief relaxation with mini-practices
Session 2	3. Activity/Rest cycles (Added: Parafunctional Habits; Masseter Massage)
Session 3	4. Pleasant activity scheduling
Session 4	5. Coping thoughts and catastrophizing
Session 5	6. Pleasant imagery and stress management
Session 6	7. Problem solving 8. Looking back and moving forward: overview and recap

6.1.2 ADMINISTRATION AND/OR DOSING

Administration and Dosing: Patients will be given 10 weeks to attend the 6 sessions. Each session will last from 60-90 minutes, depending on painTRAINER session demands. Delivery of the intraoral splint and delivery of NSAID medication will take place in the Dental Clinical Research Center operatory. Psychosocial treatment (painTRAINER) will be conducted remotely via mobile app.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Therapists. There will be no therapist involvement in this feasibility trial. All intervention activities will be managed by the painTRAINER program, plus RA tracking of TMD-specific activities.

Monitoring Treatment Integrity and Fidelity, and Patient Adherence to Treatment

The painTRAINER application records details about patient completion of modules, providing adherence data. As in the therapist-led treatments of the parent study, painTRAINER assigns practice assignments in each module.

Additional follow-up interviews will include written assessments of assignments assigned by painTRAINER and those completed. ES response rates will also be monitored via the MetricWire system by the RAs X 3 weekly.

6.3 PROTECTION AGAINST BIAS

In this feasibility trial neither randomization nor blinding of patient or research assistant is possible.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

For this treatment, participant adherence will be measured via records from painTRAINER as to assignments completed. ES response rates and tasks completed for each participant will be monitored via the smartphone app system by the RAs X3 weekly.

6.5 CONCOMITANT THERAPY

Standard Treatment (STD). The painTRAINER program will be provided alongside a standardized version of conventional conservative care for patients with TMD/Orofacial pain. Standard Treatment (STD) will consist of splint therapy plus soft diet and oral anti-inflammatory agents (Canales et al., 2016; Stack & Stack, 1992). The primary rationale for this aspect of treatment is to change the oral habits of patients with respect to clenching and bruxing, and to provide a sufficient respite from pain to allow more adaptive oral habits to emerge (despite the admitted lack of evidence for these processes). Patients will receive the intraoral splint during the first treatment visit, 1-2 weeks after the baseline visit, with instructions to keep it in place continuously (except for eating) if possible for the succeeding 4 weeks. After 4 weeks it will be recommended to patients that they start to taper the splint (e.g., use only as a night guard) in preparation for discontinuing the splint altogether. The purpose of this is to try to prevent the patient from becoming so comfortable with the splint that he/she starts clenching or bruxing on the splint itself. However, we discovered in our earlier work that many patients (~50%) elected to retain the splint and to wear it especially as a night guard, with good results, whereas others discontinued the splint as recommended (also with good results). Given the good outcomes found regardless of duration of use of the splint, we will make the recommendation for discontinuation, but not require patients to stop using the splint if they feel it is useful for them. Splint use will be monitored throughout the course of the study, and amount of use will serve as a variable for later analysis. In addition to the splint, subjects will also be given a 14-day course of non-steroidal anti-inflammatory medication (NSAIDs; naproxen sodium 550 mg po BID; or 400-600 mg Ibuprofen TID or QID; medication and dose to be determined by the prescribing dentist). Extra strength Tylenol will be substituted for naproxen for those patients who claim to have difficulty with NSAIDs or who have gastric ulcer disease, kidney disease or other contraindications. A soft diet will also be prescribed with special attention paid to avoiding foods that require extreme jaw opening (e.g., large sandwiches) or foods that have caused pain in the past (e.g., steak). Patients will be asked to continue using the splint and the soft diet until the end of the 6-week treatment period, after which they will be informed that they may alter the treatment as they see fit (e.g., discontinuing the splint), but recommending care in their diet.

6.5.1 RESCUE THERAPY

For those patients, if any, whose condition deteriorates during treatment (as reported to the RAs), referrals will be made to other providers, either inside or outside of UConn Health. Patients for whom their splints do not fit correctly, or who experience discomfort with the splint, will be seen promptly be dental staff to correct the issue.

IRB Review
IRB NUMBER: 23-052-1
IRB APPROVAL DATE: 03/29/2023

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

If a subject discontinues treatment (the intervention) but remains available for the posttreatment follow-up, that follow-up will be completed.

If a subject is scheduled for treatment but never appears, and is unable to be reached for treatment rescheduling, attempts to schedule treatment will continue for a period of 4 weeks from the date of the initially scheduled first treatment session. The subject has 4 weeks to start treatment after the first treatment session cancellation. After 4 weeks all attempts to schedule treatment will cease. Attempts will still be made to contact such persons for the posttreatment assessment.

If, during the Research Assistant's attempts to schedule the first therapy appointment, the subject says he or she no longer wants or are able to attend treatment, the subject will still be asked to participate in the research follow-up. No further attempts to schedule treatment will be made, even if 4 weeks has not passed.

All data collection will be discontinued only if the patient expressly states that he or she wishes to discontinue participation entirely, at which point all communication with that person ceases.

If a clinically significant finding is identified (including, but not limited to changes from baseline in pain or functioning) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation, pending subject agreement.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

The PI may discontinue (withdraw) a participant from the study for the following reasons:

- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation after being consented

The reason for participant discontinuation or withdrawal from the study will be recorded in the Treatment and Study Dropout database. Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

If a subject is scheduled for treatment but never appears, and is unable to be reached for treatment rescheduling, attempts to schedule treatment will continue for a period of 6 weeks from the date of treatment assignment. After that period all attempts to schedule treatment will cease. Attempts will still be made to contact such persons for follow-up assessments.

If, during the Research Assistant's attempts to schedule the first therapy appointment, the subject says he or she no longer wants or is able to follow the online treatment program, the subject will still be asked to participate in the research follow-up. No further attempts to schedule treatment will be made, even if the 6-week post randomization period has not passed.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to complete the posttreatment follow-up, and study staff are unable to contact the participant after at most 6 months.
The following actions must be taken if a participant fails to return to respond to the Research Assistant for a required study visit (in person or virtual):

- The site will attempt to contact the participant, reschedule the missed visit within a week if possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the project director or designee will make every effort to regain contact with the participant (where possible, 3 or more telephone calls., e-mails and/or texts, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to be lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Baseline session - Diagnostic Evaluation (DE). Persons meeting initial eligibility criteria will be consented and scheduled for a baseline diagnostic evaluation session. At this session baseline questionnaires will be completed remotely by the potential subjects via REDCap, with assistance from a RA by telephone (see Table 1 above) and/or WebEx conference (see Table 1 above). At an in-person clinical examination potential participants will be examined by the study dentist and oral surgeon who will rule out neuropathic or odontogenic pain and will complete the examination of orofacial pain as per the Diagnostic Criteria for TMD (DC/TMD). Following this examination prospective subjects will have a panoramic X-ray taken to rule out gross arthritic or anatomic damage to the TM joint.

Posttreatment Data Collection. At the data at which the patient should have completed 6 weeks of treatment the Patient will be asked to complete follow-versions of the dependent measures, including the pain assessments, and the process measures. This will be done remotely via REDCap surveys. At this point, patients will once again be asked to participate in ES via MetricWire for 7 days to determine if situation-specific coping has changed in treatment. $25 will be offered for Post-Tx data collection + up to $40 for Experience Sampling for 1 wk.

8.2 SAFETY ASSESSMENTS

Patient pain and functioning, along with medication usage and adherence to splint and soft diet, will be assessed at every follow-up visit by research staff, using data collection forms for this purpose. Any patient reports of pain or functioning problems will be reported to the Principal Investigator who will arrange medical/dental follow-up.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

Any untoward medical occurrence that presents during the course of a clinical investigation that might be caused by either the condition under study or by the research intervention.

Adverse events are categorized into those that are expected (predictable) and those that are unexpected (unpredictable). An adverse event is considered an unanticipated problem involving risk to subjects or others only when the event is unexpected (see definition below), related or possibly related to the research intervention (see definition below), and places the subjects or others at greater risk of harm than was previously recognized.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Those events that meet at least one of the following criteria:

- Death
- Life-threatening
- Hospitalization/prolongation of existing hospitalization

• Congenital anomaly/birth defect
• Persistent or significant disability/incapacity
• An important medical event that, based upon appropriate medical judgment, requires medical or surgical intervention to prevent one of the outcomes listed above.

A *non-serious adverse event* is any undesirable symptom or occurrence a subject experiences during participation in a clinical trial that does not meet the criteria for serious.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild:** Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate:** Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related**: The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related**: There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

Expected AEs are defined as an event that is anticipated on the basis of prior experience with the intervention under investigation or with related interventions; an event identified in the Investigator's Brochure and/or study drug labels for post marketing studies; an event that is likely due to the underlying condition of the patient being studied; or an event attributed to the patient population being studied. Such events do not require reporting to the IRB (unless the nature, severity or frequency of the events is different/greater than previously anticipated) but may require reporting to the sponsor based on terms of the clinical trial agreement and/or protocol.

Unexpected AEs include any untoward medical occurrence not listed in the protocol and the informed consent document and not anticipated on the basis of prior experience with the intervention under investigation or with related interventions; an event that cannot be attributed to the underlying condition of the patient being studied or to the patient population; or expected events with frequency and/or severity exceeding what was anticipated.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured in the Adverse Events database. Information to be collected includes event description, time of onset, RA, assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and disposition of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The project director or other trained staff will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study status meeting the investigator will inquire about the occurrence of AE/SAEs since the last meeting. Events will be followed for outcome information until resolution or stabilization.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the PI. The PI will report any SAE that is deemed related or possibly related to the study to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 7 calendar days after the investigator first learns of the event.

Any AE meeting the specified Serious Adverse Event criteria will be submitted on an SAE form to NIDCR's centralized safety system via Rho Product Safety. This report may be sent by fax or email. Once submitted, Rho

Product Safety will send a confirmation email to the investigator within 1 business day. The investigator should contact Rho Product Safety if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

SAE Reporting Contact Information:

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

The study's clinically responsible individual will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Product Safety within 7 days of site awareness.

Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within 7 days of site awareness.

All SAEs will be followed until resolution or stabilization.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

If an adverse event related to study procedures occurs to a participant the PI or another staff member will contact the participant to discuss options for that person to continue with the study or to seek additional or alternative treatment if necessary and appropriate.

8.3.8 EVENTS OF SPECIAL INTEREST

NA

8.3.9 REPORTING OF PREGNANCY

In the case of a participant reporting pregnancy, the PI will determine if the participant should continue in the study. If the participant has completed treatment and is no longer taking study medication the participant will likely continue in the study. Given the demographics of this pain problem pregnancies are not very likely.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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 Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant 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 participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the funding agency within 24 hours of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the funding agency within 5 days of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 5 days of the IRB's receipt of the report of the problem from the investigator

All unanticipated problems will be reported to NIDCR concurrently with reporting to the IRB. These reports will be made 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 UP reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

US: 1-888-746-7231

International: 919-595-6486

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

If an unanticipated problem related to study procedures occurs to a participant the PI will contact the participant to discuss options for that person to continue with the study or to seek additional or alternative treatment if necessary and appropriate.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoints:
  - Feasibility: Recruitment of 20 patients in 12 months who agree to participate in a mobile app only treatment condition
  - Acceptability: Treatment Acceptability and Adherence Scale scores
  - Adherence to Treatment: Sessions completed; Between session assignments completed.
- Secondary Efficacy Endpoint(s):
  - Pain (0-10: The average of ratings of current pain, average pain, and worst pain during the week on the Graded Chronic Pain Scale)
  - Depression Symptoms (0-60: score on the CES-D)
  - Interference with functioning (0-60: score on the MPI Interference scale); (0-200 on the Jaw Functional Limitation Scale)
- Tertiary Endpoint(s);
  - Coping Skills use (0-203, total score on the Brief Pain Coping Inventory)
  - Self-Efficacy (0-80 on the Facial Pain Self-Efficacy Scale)
  - Momentary coping instances (per Experience Sampling)
- Other Tertiary/Exploratory Endpoints: Somatization; Catastrophization;

9.2 SAMPLE SIZE DETERMINATION

Power Analysis

This is a one-condition design. The number of participants needed for this feasibility study was determined by the need to establish feasibility and acceptability of treatment. For the most part these are subjective standards. However, 20 additional participants recruited in 44 weeks (i.e., allowing for all to have 6 weeks of treatment plus a follow-up) will be sufficient to establish our ability to recruit for this type of intervention. Likewise, we expect to retain at least 80% at posttreatment within a 95% confidence interval of +/- 20%. (In actuality, our typical retention rate is much better than this: 87+% at post). This number of patients will also be sufficient to establish equivalence of credibility between the MobileApp and the two therapist-led treatments (hypothesis 1).

The test of credibility was based on a two-group design, such that the MobileApp condition is compared to a group comprised of patients from the other two treatment conditions. Specifically, power was ascertained based on a test of equivalence between the MobileApp condition and the therapist-led conditions on treatment credibility, based on between-treatment credibility data provided by Arch et al. (Arch et al., 2012). An equivalence test of means using two one-sided equal-variance t-tests with equivalence limits of -2.5 and 2.5, an actual difference between the means = 1.1, and a standard deviation = 1.7, would require sample sizes of 19 in each group to achieve 81% power at a 5.0% significance level. (Analysis based on output from Pass 2019).

9.3 POPULATIONS FOR ANALYSES

Intention-to-Treat (ITT) Analysis Population (i.e., all participants assigned to treatment)

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

- Acceptability will be assumed if 80% of patients assigned to treatment agree to participate in the painTRAINER program.
- Acceptability and Credibility scores will be compared with published norms.
- Credibility/expectancy (CEQ) scores will also be compared to those from the two parent study conditions, using a non-superiority analysis.
- Adequate Adherence will be declared if patients complete 80% of planned assignments

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

H1: The mobile application (painTrainer) will prove to be a feasible and acceptable intervention.
20 patients will be recruited and treated within 42 weeks, and we expect 80% of patients to complete at least 3 of the 6 planned modules. No additional analysis is planned for this hypothesis.

H2a. The mobile application (painTrainer) will prove to be a credible treatment. Scores on the treatment credibility measure (the treatment credibility/expectancy questionnaire; CEQ) will be computed for the MobileApp patients and compared to means published by Devilly and Borkovec, (Devilly & Borkovec, 2000). Scores like those in the general range (i.e., within 2 SD) of those reported by Devilly and Borkovec will be considered as indicating that the STD+MobileApp condition is credible.

H2b: The mobile application (painTrainer) will prove to be as credible as the therapist-led treatments currently provided in the Parent study, as demonstrated by tests of non-inferiority on credibility scores. Tests for equivalence of means will be conducted on the posttreatment mean scores for the CRE from the MobileApp patients (n=20) and from the two therapist-led conditions (n=20 total). The Equivalence Tests for Differences Between Two Independent Means, or the Two One-Sided Test (TOST) procedure, entails performing two one-sided tests to examine whether the observed data are surprisingly larger than an equivalence boundary lower than zero (ΔL) or surprisingly smaller than an equivalence boundary larger than zero (ΔU) (Schuirmann, 1987). In this case the symmetric range of -2.5 to 2.5 is based on differences observed by Arch et al. (Arch et al., 2012). If both tests fail to show significant differences between the MobileApp and the combined means of the two therapist-led conditions then we may claim that the CEQ means are “equivalent” (though we may not declare the conditions “the same”). That is, failure to find mean between-group differences on credibility, given these constraints, would suggest equivalence of means on this measure.

H3. Patients in the MobileApp will show acceptable adherence to the scheduled procedures, as evidenced by scores on a treatment adherence measure, and through completion of sessions (> 3 of 6 planned modules) and exercises monitored by the painTRAINER mobile app (i.e., > 80% completion of recommended exercises), as well as those exercises administered and monitored by the RAs (>80% of worksheet and other exercise completion).

RESEARCH STRATEGY

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Analysis of Secondary endpoints will entail comparisons of secondary and tertiary endpoint variables from this study with the same variables from the conditions in the parent study, using t-tests and univariate ANOVA. Due to the small N of this study, these analyses will not be cited as evidence of differences (or lack of differences) between this intervention and the therapist-led interventions.

9.4.4 SAFETY ANALYSES

Pain will be tracked at every treatment (by the painTRAINER app) and follow-up visit. Adverse and Serious Adverse events will be tracked to determine whether online treatment yields an unusual number of such events.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be summarized.
At a later date the baseline characteristics of this sample will be compared to those of the two parent study condition samples, using individual t-tests and chi-square tests.

9.4.6 PLANNED INTERIM ANALYSES

None

9.4.7 SUB-GROUP ANALYSES

No sub-group analyses are planned at this time.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

Additional between-subject analyses. Analyses of a more exploratory nature will also be conducted on between-subjects variables. These analyses will include the effect of dispositional moderators such as somatization, catastrophization, acceptance and neuroticism on pain and adherence. Another analysis will separate those whose pain is extremely variable from those whose pain is stable at pretreatment to determine if these represent different types of patients.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant, and documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

*Consent Form

*HIPAA form

*These will be administered remotely. Potential participants will have access to forms via links to REDCap. Electronic signatures will be logged and saved.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Recruitment and screening. Patients will be recruited both through the University dental clinics and through newspaper, radio and internet advertisements. Persons will respond to the advertisement by telephone. Those who call will be told that the purpose of the project is to test different TMD treatments. Those interested will be screened over the telephone for basic inclusion/exclusion criteria. Those who meet eligibility at this point will be scheduled within 14 days for a diagnostic evaluation (DE). Persons meeting initial eligibility will come to the Health Center for the DE.

Consent Process. Prior to any activities the person will be administered the Consent Form, and the project will again be described. The consent process will be conducted by the Research Assistant (RA) by telephone. This phone call will either be conducted immediately after the prospective participant passes the Quick Screen, or at a later time arranged between the person and the RA. The consent form will be sent to the prospective participant via REDCap link sent by e-mail. While on the telephone the RA will assist the prospective participant with opening the REDCap link and will stand by while the person reads the Consent Form, and will explain any parts of the Consent Form about which the person has questions. Those who then still agree to participate will be asked to sign the Consent Form. Study procedures will not proceed until a copy of the consent, electronically signed by both the participant and the consenter, have been merged and a signed copy returned via e-mail to the participant

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily 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 to study participants, investigators, UConn Health Research Administration, UCH IRB, and the funding agency. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitors, and the funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

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

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at an appropriate national Data Coordinating Center. This information will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Data Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Data Coordinating Center.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies. It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see https://grants.nih.gov/policy/sharing.htm). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the UConn Health General Clinical Research Center. When the study is completed, access to study data and/or samples will be provided through UConn Health General Clinical Research Center. Those wishing access to the data will apply to the Principal Investigator, who will authorize access to qualified investigators with legitimate scientific questions.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor or Independent Safety Monitor**
Mark D. Litt, PhD Professor and Principal Investigator	Seema Kurup, Department of Oral Diagnosis
UConn School of Dental Medicine	UConn School of Dental Medicine
Division of Behavioral Sciences & Community Health	Division of Oral and Maxillofacial Surgery
860-679-4680	860-679-3300
LItt@uchc.edu	Dshafer@uchc.edu

10.1.6 SAFETY OVERSIGHT

In addition to the PI's responsibility for oversight, study oversight will be under the direction of a Data and Safety Monitoring Board, which will meet at least annually throughout the course of the study.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, with International Council on Harmonization Good Clinical Practice (ICH GCP) guidelines, and with applicable regulatory requirements.
Monitoring activities will be as follows:

- Research Assistants or the clinical coordinator (throughout the study), will monitor patient pain, behaviors and complaints. Monitoring will be at least weekly during the treatment phase, and at the posttreatment follow-up. Any indication of patient safety being at issue will be immediately reported to the PI and to the Project Coordinator for assessment of needs and remediation if necessary.
- Independent audits may be conducted by the UCH IRB to ensure monitoring practices are performed consistently.
- NIDCR and its designees will conduct regular clinical monitoring.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data collection, documentation and completion. We will follow a common quality management plan.
Quality control (QC) procedures will be implemented as follows:
Informed consent - Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data - Data will be initially captured on source documents (see *Section 10.1.9, Data Handling and Record Keeping*) and will ultimately be entered into the study database using REDCAP. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity - Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in *Section 6.2.1, Interventionist Training and Tracking.*

Protocol Deviations - The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern. Any protocol deviation caused by study personnel will be reported immediately to the UCH IRB for review.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities, in this case, UCH IRB.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff under the supervision of the Principal Investigator. The Principal Investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.
All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

When necessary, hard copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents. All other patient reports will be entered directly in the REDCAP system.

Clinical data (including AEs) will be entered into a tracking database. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents and/or from patient reports.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last follow-up has been recorded. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.
These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the Principal Investigator to identify and report deviations from the clinical protocol. All deviations will be recorded in the study tracking database within 2 days of study staff becoming aware of them, and reported to the UCH IRB and to NIDCR on an annual basis. The process for identifying protocol deviations is described in detail in a separate Data Quality Monitoring Plan.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- National Institutes of Health (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.
- This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 1 year after the publication of the main trial results. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIDCR has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

None

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CBT	Cognitive-Behavioral Therapy
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
ES	Experience Sampling
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IATP	Individualized Assessment and Treatment Program
ICH	International Council on Harmonization
IRB	Institutional Review Board
ITT	Intention-To-Treat
MLM	Multilevel modeling
NIDCR	National Institute of Dental and Craniofacial Research
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RA	Research Assistant
SAE	Serious Adverse Event
SOA	Schedule of Activities
STD	Standard Treatment
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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