Nonpharmacologic Reduction of Periprocedural Pain, Anxiety, and Prescription Drug Use

Study Chairman or Principal Investigator:

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Tool Revision History

Version Number 3:
version Date: 10/26/2017
Summary of Revision Made:

Added a +/-2min window for collection of the q10 min data on the dental chair to avoid protocol violation in case the dental procedure results in expected or realized delay of sampling

Version Number: 2
Version Date: 9/8/2017
Summary of Revisions Made:

More detail and validation provided for scales used
Approach to intermittent missing data inserted

Version Number: 1
Version Date: 8/31/2017
Summary of Revisions Made:

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STUDY TEAM ROSTER

This is a clinical trial under the auspices of an SBIR grant to the applicant organization Hypnalgesics, LLC with the Principal investigator, Elvira V. Lang, MD and is conducted at the Tufts School of Dental Medicine in Boston with the site Principal Investigator Roald J. Kulich, PhD (Ronald.Kulich@tufts.edu).

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PARTICIPATING STUDY SITES

This is a single center study. The study site is Tufts University School of Dental Medicine**,** One Kneeland Street, Boston, MA 02111. Tel: (617) 636-2147, Fax: (617) 636-3511. The principal investigator at the site and site address is Ronald Kulich, PhD (Ronald.Kulich@tufts.edu).

PRÉCIS

Study Title

Nonpharmacologic reduction of periprocedural pain, anxiety, and prescription drug use

Objectives

Objectives of this Phase I pilot trial are to provide data towards assessing and facilitating feasibility of a larger scale Phase II trial in which the effects of a calmative Comfort Talk® app can be unequivocally evaluated.

Towards this goal we will pursue following outcome parameters for

Phase I: Feasibility/acceptability assessment:
Primary outcome parameter:

- ability to obtain complete on-site data sets from at least 90% of patients enrolled (with at least 40% from patients in the app group and at least 40% from patients in the control group).

Secondary outcome parameters:

- ability to enroll 60 patients by day 150 after initiation of recruitment in the clinic (=day 1)
-
- Obtain 38 packages of filled out diary cards (at least 16 from patients in the app group and at least 16 from patients in the control group)

- 90% of patients in app group listen to app ≥5 min

Phase II preparation

primary outcome parameter

- anxiety at the end of the waiting room time

Secondary outcome parameters

- pain the end of the waiting room time
- anxiety during treatment
- pain during treatment
- anxiety during 1 week after treatment
- pain during 1 week after treatment
- use of units of sedatives and analgesics during 1 week after treatment
- patient satisfaction

Design and Outcomes

The design is a single-blind, placebo controlled clinical trial to test the feasibility of the trial design assessing the ability of a Comfort Talk® app to nonpharmacologically reduce anxiety, pain, and periprocedural drug use in individuals 18 years of age and older undergoing outpatient treatment in the Craniofacial Pain Center of the Tufts School of Dental Medicine.

The trial is a single-site pilot trial to assist in sample size estimation in a pivotal trial to test the hypothesis that listening to a Comfort Talk® app with calmative content reduces pain, anxiety, and post-procedural medication use.

Eligible patients at the Craniofacial Pain Center at the Tufts School of Dental Medicine (TUSDM) will be randomized to listen to a tablet containing a calmative Comfort Talk® app or app with white noise on an intent-to-treat basis. Their anxiety and pain measures will be recorded on validated 0-10 scales and before listening, at the end of the waiting room period, and every 10 minutes (+/- 2 minutes) while on the dental chair.

All patients will be given a packet with diary cards to record their levels of anxiety, pain, and drug use daily for 7 days after their visit and asked to send those back. Subjects will be mailed a $25 check upon returning their diaries.

Patients randomized to the Comfort Talk® app will receive a download coupon for the app before leaving TUSDM, those randomized to the control condition (white noise) will receive a download coupon after they send in their diary cards.

Interventions and Duration

Approximately 1 hour and 15 minutes (Up to 30 minutes more than the scheduled standard of care visit, which will typically last up to 45 minutes):

Patient will be asked to come in ½ hour early before an already scheduled appointment. They will be taken to a private area, report their demographics, and if eligible consented and fill out a NIDA Quick Screen.

The participant will then be verbally asked to indicate his/her pain and anxiety levels on validated 0-10 scales. The research assistant will then hand the participant a tablet containing, depending on the group attribution, either the app (App Group) or white noise (Control Group) and will be shown how to operate the tablet.

Participant will then return to the clinic waiting area with the tablet and wait for their regularly scheduled appointment. The patient will be at liberty to when and for how long to listen. At the end of the waiting room period the participant will be queried again for their levels of pain and anxiety.

After the participant enters the treatment room, he or she will be able to continue to listen to the app or white noise on the tablet. The research assistant will ask the participant every 10 min (+/- 2 minutes) to indicate their pain and anxiety levels. The research assistant will note the duration of chair time, the amount of lidocaine given, if any or which other medications were given during the appointment, and whether the dental practitioner prescribed opioid, prescription or non-prescription drugs at the end of the visit.

Before leaving home, the participant will be asked to fill out a satisfaction survey based on a modified Press Ganey Template. The participant will then receive a diary card on which to note pain, average and maximal pain as well its location, use of non-prescription, prescription, and opiate drugs, use of the app, and be provided pre-stamped envelopes. Patients will be asked to complete the diary daily before bedtime for 7 days.

Sample Size and Population

The pilot will be conducted in the Craniofacial Pain Center of TUSDM. Patients included in the trial will be those who come for the procedures offered in the Craniofacial Pain Center such as fitting and adjusting dental bite appliances, fitting and adjusting oral appliances for management of sleep apnea, trigger point therapy, botulinum toxin therapy, and various craniofacial and cervical nerve blocks for pain management. Procedures last on the average 45 min.

Subjects will be randomized to one of four tablets using a randomization plan generated by SAS version 9.4 PROC PLAN. Given that four tablets will be available at one time, four subjects will be randomized per block. Given a total sample size of 72, subjects will be randomized to 18 blocks.

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective concerns feasibility/acceptability of the trial design. This will be assessed by the ability to obtain complete on-site data sets from at least 90% of patients enrolled (with at least 40% from patients in the app group and at least 40% from patients in the control group).

1.2 Secondary Objectives

Secondary objectives further assess overall feasibility of the trial design and aim to obtain sufficient data to assess the ability to calculate reliable sample size requirements for Phase II.

Feasibility parameters:

- ability to enroll 60 patients by day 150 after initiation of recruitment in the clinic (=day 1)
- Obtain 38 packages of filled out diary cards. (at least 16 from patients in the app group and at least 16 from patients in the control group)
- 90% of patients in app group listen to app ≥5 min

Since a significant reduction in anxiety in the waiting room is the main ingredient that underlies all other hypothesized effects for Phase II outcomes, even in the face of proven technical feasibility of trial execution, it was also taken into consideration for sample size calculations.

We hypothesize that use of the active Comfort Talk® app results in a reduction in anxiety by 35% at the end of the waiting room time. This degree of reduction in anxiety is clinically significant based on prior work in a clinical trial that demonstrated that a 35% difference in anxiety at the onset of an invasive medical procedure is associated with significant differences in the subsequent experience of pain and anxiety during the procedure, need for opioid analgesics and sedatives, and the overall length of the procedure (1). These factors directly affect procedure safety and throughput (e.g. economical efficiency).

Secondary clinical outcome parameters will be:

- anxiety at the end of the waiting room time
- pain the end of the waiting room time
- anxiety during treatment
- pain during treatment
- anxiety during 1 week after treatment
- pain during 1 week after treatment
- use of units of sedatives and analgesics during 1 week after treatment
- patient satisfaction

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

In the US, >100 Million surgical and >300 Million dental procedures are performed annually (2-4). An estimated 20 to 30% of patients fear these procedures, and 8.75% severely so (5, 6). Thus a considerable faction of the population is affected. Some patients don't keep their appointments, delaying treatment (5, 7-11). Others who present for their procedures are distressed in the waiting room (see also 2.2).

Healthcare professionals mainly rely on opioids and sedatives for management (12, 13). However, even under medical supervision during procedures and with dosages usually well tolerated, these drugs can cause cardiovascular and respiratory compromise and death (14). Of concern is the increasing practice of IV sedation in dental offices, which typically lack resuscitative experience (11). Drugs prescribed to manage pain after discharge feed into the opioid epidemic. Every day 80 people die from overdoses, half of them caused by prescription drugs (15).

The majority of surgeries are now performed in outpatient settings (16). At discharge, typically neither doctors –nor their patients– know what the patients' analgesia needs will be during recovery. Ample amounts of opioids are then prescribed as a time-saving solution. Particularly patients who didn't learn how to deal with potentially painful sensations during general anesthesia then can suddenly find themselves at home unprepared to cope. In one study, such patients used 8x the amount of morphine equivalents (23.9 vs 3 mg) their counterparts took who were awake and had to cope during their surgery (17). Comfort during and after conscious surgery, however, requires well-developed coping skills (17-20), or external guidance therein. Our prior large-scale clinical trials showed that guiding patients in self-hypnotic relaxation at the onset of invasive medical procedures can provide such coping skills. The results were sustained reductions in pain and anxiety; drug use, complications, procedure time, and cost decreased while satisfaction increased (21-24). The benefits of such live-guided interventions have also been shown by other researchers (25-42). Trained personnel to provide such services, however, are not widely available. Empowering patients directly with a validated app that they can adjust to their needs in the moment is a desirable alternative.

The long-term goal is to provide a validated practical means of non-pharmacologic reduction of pain, anxiety, and need for post-procedure prescription drugs achieved through a Comfort Talk® app for the patients undergoing these procedures. Our large-scale clinical trials showed that short Comfort Talk® scripts spoken live by trained personnel at the beginning of invasive procedures change the mode of distress processing with a sustained reduction in pain and anxiety (21, 22, 24). Also drug use, complications, and procedure time significantly decreased while patient satisfaction and operational efficiency increased. Comfort Talk verbiage used live by MRI personnel resulted in significantly more patients keeping their appointments and completing their examinations (7). An app that could provide similar benefits is highly desirable. While the Comfort Talk® app approach will be applicable to procedures in general, dentistry is chosen as the test environment. Dentistry is not only a

common source of anxiety and pain but also ranks as the second largest prescriber group of addictive drugs.

2.2 Study Rationale

Scientific Premise

The app is designed for use by individuals awaiting medical/dental procedures. After choosing the options on the Comfort Talk app, the patient listens to the recording via earphones. Specifically the study will be performed in the dentistry waiting room.

The text content of the Comfort Talk® app is based on clinically-tested scripts which were validated in three large-scale, federally-funded, clinical trials with 678 patients in randomized sequence and published in peer-reviewed journals (21, 22, 24). Use of these scripts with patients at the time they presented for medical procedures was associated with significant reductions in pain, anxiety, need for narcotics and sedatives, and adverse effects. Live use of the script language and word snippets developed in clinical practice by medical personnel was further tested with patients presenting for MRI scans in a multicenter trial encompassing a total of >97,000 patients. Having personnel trained in using live Comfort Talk scripts and word snippets was associated with a significant reduction in non-completion of scans due to claustrophobia and disruptive patient motion compared to baseline cases without training and use (7). In a further randomized trial assessing the effect of training personnel in delivery of script elements, trained sites had more efficient patient throughput, a lower no-show rate, greater patient satisfaction, and overall higher patient volume (43).

Our research showed that being in a waiting room is fraught with considerable distress for a patient based on a study with 214 women who were awaiting either a diagnostic procedure (breast biopsy), invasive embolization of benign uterine fibroids, or a higher risk and invasive chemoembolization of malignant liver cancers (44). All three patient groups experienced abnormally high mean scores on Perceived Stress, Impact of Event, and Center for Epidemiologic Studies Depression Scales. The diagnostic breast biopsy group had the highest anxiety levels which were elevated to an abnormal level. One may conclude that the uncertainty of diagnosis in that case was associated with greater stress than was awaiting more invasive and potentially higher risk treatment. The adverse impact of uncertainty was also borne out in another study that showed that waiting after a biopsy for days without knowing the diagnosis resulted in abnormal stress responses similar to having been informed of a cancer diagnosis, as measured by salivary cortisol profiles (45).

In case of uncertainty and ambiguity, the natural mental processing is geared to choose the more negative interpretation, such as pain or danger (46, 47). Once a painful stimulus has occurred one also tends to be more attentive to external cues that could indicate pain, even when there is none (48). Expectancy then further shapes pain-intensity processing in the brain (49).

The mechanism by which the app-delivered verbiage is postulated to reduce pain and anxiety was elaborated in prior large-scale clinical trials evaluating procedures of varying degrees of invasiveness and procedural risk: outpatient large core breast biopsy performed with local

anesthetic only (21), vascular and percutaneous renal interventions performed with access to IV conscious sedation (24), and tumor embolizations performed with conscious sedation which are higher risk procedures that induce tissue ischemia (22).

Three essential premises underlie the mechanism of action:
1. Under standard care conditions, acute anxiety and pain increased linearly over time as is evident in Fig. 2-3. The steepness of the pain curve was relatively independent of stimulus severity and medications administered, and was indistinguishable among three types of procedures of vastly different invasiveness and risk (50). Time zero on Figs. 2 and 3 was patient entry into a procedure suite and initial preparation and positioning. Based on our work in the MRI setting, we speculate that the increase in pain and anxiety also happens when a patient is not instrumented, and thus the length of time becomes the limiting factor in the patient's intolerance for remaining on the examination table (7).

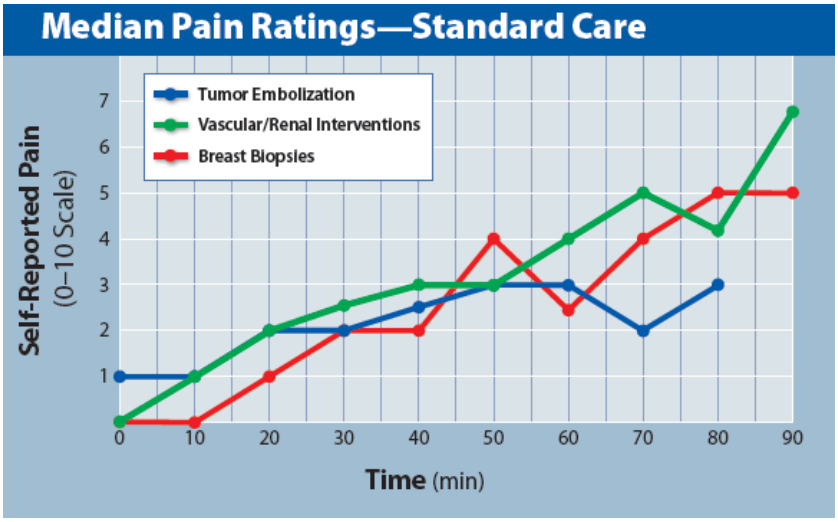

Fig. 1: Course of pain perception during procedures of widely varying invasiveness and potential for pain stimuli (from (50)).

2.) When patients were read a short 1-3 minute self-hypnotic relaxation script by trained personnel *at the onset* of these procedures, pain no longer increased over time in all three trials, even in procedures that lasted hours (Example, Fig. 2) This implies that **a fundamental and sustained change in the mode of processing pain and anxiety can be achieved through a short set of suggestions at a time when the patient is exposed to an ambiguous situation and potentially painful stimuli**. In cases performed under IV conscious sedation, patients in the script group also requested and received significantly lower doses of sedatives and narcotics and had more stable vital signs, fewer complications, and shorter procedures times.

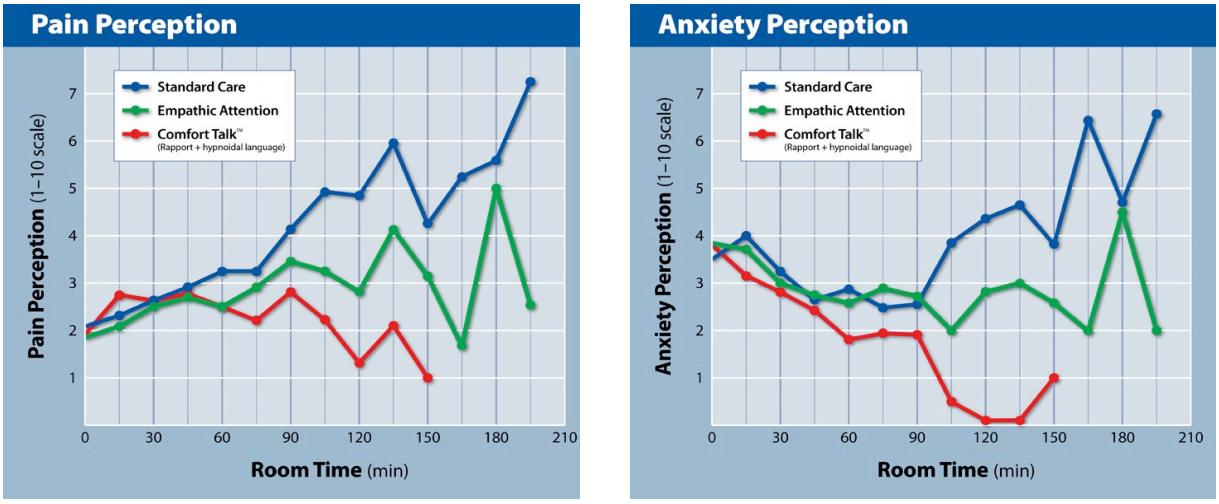

Fig. 2: 1-3 minutes of comforting words (red line) at the onset of renal/vascular procedures prevented the naturally occurring increase in anxiety and pain over time under standard care conditions (blue line) and allowed procedures to be completed faster (from (24)).

Use of a self-hypnotic relaxation Comfort Talk® script or Comfort Talk snippets of helpful suggestions and hypnoidal language also had significant benefits when delivered live by trained MRI personnel. In a clinical trial with 97,712 patients, incompletion scans due to claustrophobia and disruptive patient motion decreased significantly from 2.3 pre Comfort Talk® training to 1.4% post training, indicating improved patient tolerance (7). Two sites in this trial (Tufts Medical Center and The Ohio State University Hospital MRI) used this benefit additionally to perform more lengthy and combined procedures.

In a subsequent trial six MRI sites were randomized to receive training in delivery of the language elements provided in the app. in the setting of a saturated market, three sites were trained, three were not. Analysis of 27,425 patient visits showed better patient retention, attendance at examinations, improved throughput and satisfaction with treatment in the trained sites compared to non-trained sites (43).

Better patient tolerance is also reflected in a current clinical trial, funded by NCCIH-SBIR R44 AT006296 with 29,772 patients at Duke University MRI. Enabling personnel to deliver the verbiage snippets by script or conversationally also resulted in significant reductions in 1.) patients' use of oral sedatives in the waiting room, 2.) extra time due to patient disruptive motion or claustrophobia, and 3.) MRI study incompletions (Fig. 3).

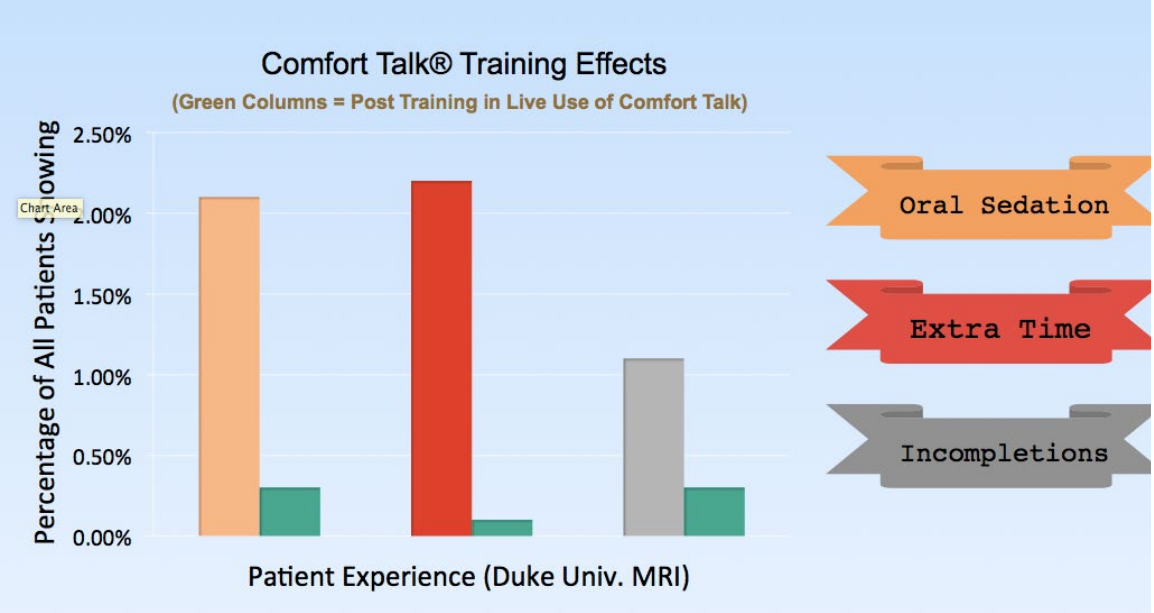

Fig. 3 Data obtained at Duke Medical Center MRI before and after Comfort Talk training enabling personnel to deliver verbiage integrated in the Comfort Talk app

3.) Elevated anxiety levels immediately prior to invasive procedures are a predictor of higher anxiety and pain during procedures, need for drugs, and procedure time (1). These findings concur with reports that identify anticipatory anxiety right before surgery and/or interventions as a predictor of poor patient compliance, greater pain, poorer outcomes, delayed recovery, and maladaptive postoperative behavior (1, 18, 51-61). A validated patient Comfort Talk® app, that patients can use to assist with coping in the waiting room, thus promises to not only benefit the patients but also the healthcare professionals and social environment they engage with.

Administration of Intervention

The app will be delivered via earphone in the waiting room to patients who are randomized to the test group. A tablet is offered to the patients on an intent-to-treat basis e.g. patients can listen as much or little as they wish.

Sample screens are shown below, as described in the legend for Fig 4. Upon opening the app, the user will begin with Figure 1a which is the static Home screen. It has an overview, links to the Background and Legal screens, and a Begin bar. Pushing the Begin bar leads to Figure 1b which shows the Selection screen with 4 options (Relaxation, Confidence, Comfort, Peace). When the user pushes one of the selections Figure 1c, the Personalization screen appears. On the Play screen the user has the option to choose among one of four voices, between a long or short version of the script indicated by Talk Time, and can add Extras to extend the Talk Time. The expected final Talk Time is reflected on the bottom Play bar which also displays the customary player symbols for start, stop, and location indicator of the recordings. Once the user pushes the play symbol the audio delivery starts. The user can stop the play by pushing the square stop symbol, repeat, restart with the same or different settings from the Personalization screen, or return to the Selection screen to listen to a different selection. The chosen selections do not auto-repeat.

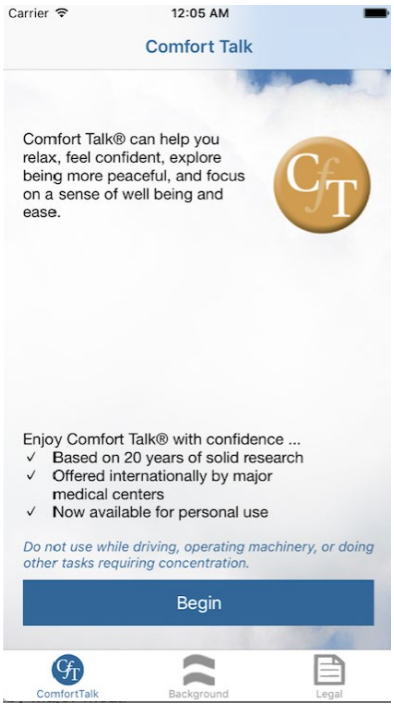

Fig. 4 a
Home screen with Background and Legal screen links. Pressing "Begin" links to the screen in Fig 1b.

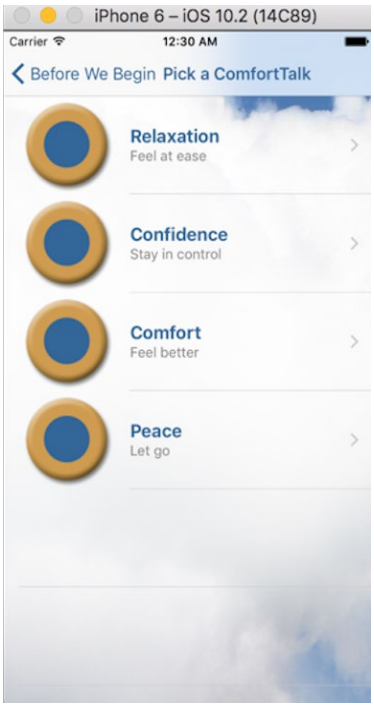

Fig. 4b
Selection screen showing a choice of 4 topics. Pressing "Relaxation" links to upper screen in Fig 1c.

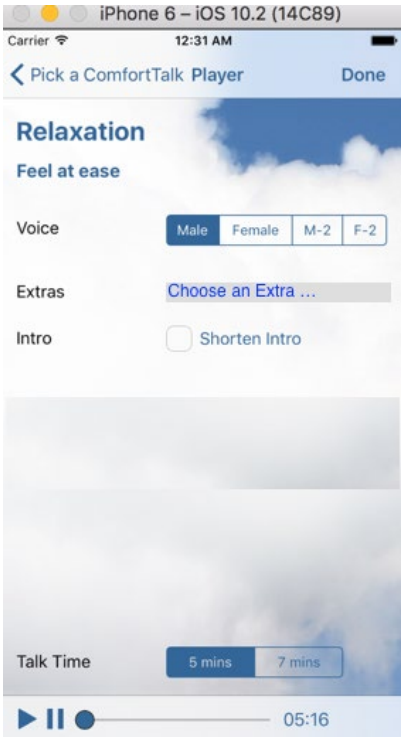

Fig 4.c Sample of a Personalization screen to choose Voice, Extras, and Length of Talk time. Play bar at the bottom of the screen

The shortest combination of listening content is 5 min. With different choices, voices, and extras the participant can extend listening time for as long as desired.

Even though live use of the app segments by medical personnel has been shown in prior trials to be effective in as little as 90 sec segments, 5 min listening time was chosen as criteria of feasibility success per NCCIH recommendation.

Risks

The risks of the standard of care dental procedures in the TUSDM Craniofacial Pain Center are not increased or affected as a result of participating in this study.

Patients who are randomized to one of the control group and who are anxious may be disappointed for not getting the app while waiting.

Because any dental procedure with or without the app can cause increasing anxiety and pain, anxiety and pain will be monitored at frequent intervals with validated 0-10 verbal assessment scales during their clinic visit. The investigators at the Craniofacial Pain Center at TUSDM are furthermore experts in managing patient's pain and distress and assure (as they do for all their

patients) that they leave with acceptable comfort levels. Dr. Kulich and Jackson are furthermore psychologically trained and will be able to recognize any unexpected AEs related to participating in the study.

When patients hear drill sounds or had prior traumatic experiences and the environment suddenly reminds them of those they can vividly relieve the old trauma. This is very rare in a dental setting and can occur whether patients would listen to an app or not. A very unlikely risk could conceivably be a scenario in which a person with active multiple personalities or active psychotic disease that may not have been obvious or known or treated prior to training becomes revealed. In these cases the individual would be evaluated by the psychologists on staff at the Craniofacial Pain Center and referred for treatment.

3. STUDY DESIGN

1. This is a single-blind placebo controlled trial comparing a Comfort Talk® calmative app (App Group) with a white noise app (Control Group).

2. Primary outcome parameter will be ability to obtain complete on-site data sets from at least 90% of patients enrolled (with at least 40% from patients in the app group and at least 40% from patients in the control group).

Secondary Feasibility parameters will be:

- ability to enroll 60 patients by day 150 after initiation of recruitment in the clinic (=day 1)
- obtaining 38 packages of filled out diary cards (at least 16 from patients in the app group and at least 16 from patients in the control group)
- 90% of patients in app group listen to app ≥5 min

Phase II outcome parameters:

Primary: anxiety at the end of the waiting room time.
Secondary:

- pain the end of the waiting room time
- anxiety during treatment
- pain during treatment
- anxiety during 1 week after treatment
- pain during 1 week after treatment
- use of units of sedatives and analgesics during 1 week after treatment
- patient satisfaction

3. Study population: 72 eligible patients (36 test group, 36 control group)

4. Study location: Outpatient clinic at TUSDM

5. Enrollment period and follow-up time:

- For individual patients: time of clinic visit data collection on site plus 7 days at home follow-up by diary card
- For the entire trial: 6 months

6. Description of intervention: The research assistant will hand the participant a tablet containing, depending on the group attribution, either the app (App Group) or white noise (Control Group) and will be shown how to operate the tablet.

Participant will then return to the clinic waiting area with the tablet and wait for their regularly scheduled appointment. The patient will be at liberty to when and for how long to listen.

7. Randomization, blinding and any stratification:

We will use 4 tablets, two with Comfort Talk® app, two with white noise, labeled A,B,C,D. The tablets will be preloaded with the respective content in a randomized sequence at Hypnalgesics, unknown to the Tufts investigators.

Dr. Jackson/research assistant will consent the patients, hand the patient the tablet based on the randomization scheme (which will be provided by Drs. Finkelman and Roomian), obtain baseline data, query and record trial data but **will not analyze** data. There is a possibility that he may become unblinded, however he will not share his observations with the analyzing team.

Strict blinding will be maintained for the analyzing team. Analysis of data will be performed by the statisticians Drs. Finkelman and Roomian, who will remain blinded throughout the trial as to which tablet contained which content. They will not have any patient interactions and thus also will also not be privy to any accidental unblinding of tablet content during the dental treatment.

8. n/a

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

- Male or female patients age 18 years and older
- Scheduled to undergo a dental procedure at the Craniofacial Pain Center
- Able to hear, write and read in English, as the ComfortTalk® scripts, study scales and take-home diary are in English
- Able to operate a standard smart tablet or smart phone and have access to a smart tablet, smart phone at home, or computer-based app download
- Willing and able to give informed consent

Contraception will not be necessary for participation in the trial.

4.2 Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation:

- Known acute psychiatric disorder, such as multiple personalities which will be assessed on the medical history form
- Not meeting inclusion criteria

Subject Withdrawal/Termination Criteria

- Subjects who do not comply with the study procedures, such as not returning diaries
- Subjects who decide to stop participating in the study will be withdrawn. These subjects will not be further asked for their pain and anxiety measures, but whichever data they have contributed will be entered in analysis.

The Site Principal Investigator will determine whether subjects (either withdrawn subjects or subjects completing the study) are in need of additional treatment and/or follow-up observation as a result of participation in this trial. Subjects and/or their insurance will be responsible for the cost of any standard of care follow-up visits or additional treatment that is not part of this study.

If a subject withdraws or is withdrawn, any data collected up to that point will still be used for the study. However, no further data will be collected for that subject.

Status of contraception and pregnancy are not considerations.

4.3 Study Enrollment Procedures

Candidate Identification and Recruitment

The Tufts study team will review the Craniofacial Pain Center schedule to identify patients that are at least 18 years of age with an upcoming visit. Potential subjects will be contacted via phone by a research team member prior to their upcoming visit to introduce the study, using an IRB-approved phone script. If the patient is interested in participating in the study, they will be asked to come into the clinic half an hour before their scheduled appointment. This half hour will be used to consent the participant, and complete randomization.

Patients who present at the Craniofacial Pain Center may also be approached by a member of the research team, and asked for their interest to participate.

Paper flyers will be posted throughout the Craniofacial Pain Center at TUSDM. Permission is not required for these posting locations. Flyers will remain posted until enrollment goals are met.

All of the forms of recruitment have been submitted to the Tufts IRB and been approved on 7/20/2017.

A screening interview/questionnaire or screening script will be used for recruitment.

Screen failure data will be retained by site-PI. Screening ID number and demographic information will be recorded. Identifiable information will not be recorded in the Screening Log.

Informed Consent/Assent

The site-PI or his representative will introduce the study. The site-PI or her representative will obtain informed consent/assent following SOP: Written Documentation of Consent (HRP-091). Consenting will take place in a private area and the patient will be given as much time as he/she needs to consider participation. The participant will be invited to include or exclude any associates (e.g., loved ones) in the consent process. Patients will be asked to read the consent form and given ample opportunity to have their questions answered. To avoid coercion, the consenting investigator will read through the copy of the consent form with the participant section by section, making sure the participant understands each section and has an opportunity to ask questions. If at any time the participant indicates s/he is not interested in participation, the meeting will end.

Informed consent will be obtained from the subject. The purpose and nature of the study will be reviewed and explained to all potential subjects by the site-Principal Investigator or Co-Investigator. The subject will be given a consent form to read, after which they will be asked whether they have any questions. When all questions have been answered to the subject's satisfaction, they will be asked to sign the consent form should they be willing to participate. A copy of the consent form will be given to each subject. If any new finding requires any change to the informed consent form, the subject will be re-consented.

Non-English speaking subjects will not be enrolled in the study because study staff at this time are not certified, prepared, or trained to translate or communicate in any language other than English. The study budget does not allow for the payment of translation services at this time. There are no direct benefits to this population by participating in this study.

Patients will be given the Tufts University approved consent form. Only adults who can consent for themselves will be enrolled, not those requiring consent from a legal representative for adult patients.

Randomization for Patients

Four tablets were preloaded by Hypnalgesics with the app or white noise in a randomized sequence that is unknown to the Tufts team to maintain blinding of the site investigators. To sets of sealed envelopes, numbered from 1-80, are provided to the site investigators. One set contains for use of the research assistant contains a card with A,B,C, or D based on the randomization sequence provided by Drs. Roomain generated by SAS version 9.4 PROC PLAN. This envelope will be opened after the patient has been screened and consented. Then the research assistant will hand the patient the respective tablet labeled A,B,C, or D.

Hypnalgsics, LLC will also have prefilled and sealed the second set of envelopes with the same 1-80 numbering sequence which, according to group attribution, will contain either a download coupon for patients receiving the test tablets, and a thank you note and information

that they will receive their download code after they send in their questionnaire for control patients. This envelope will be provided to the participant when they turn in the devices before leaving the clinic.

All patients sending back their diaries will receive the download coupon with their check. This will lead to some duplication for the test patients who already had received a download coupon at the time of their clinic visit but this will maintain blinding of study personnel.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The app is a non-Significant Risk Device (NSR). It does not perform diagnostic tasks or tie in with a device that requires FDA clearance (such as apps aiding in ECG interpretation or detection of skin malignancies). Review of the Human Subjects component by the NIH for this grant proposal resulted in "Human Subjects: Certified, No concerns" in the Summary Statement.

Group	Intervention
Experimental	Electronic Tablet Comfort Talk® appRv2
Control	Electronic Tablet White Noise

Patients will be given a tablet containing either the app or white noise control content during their clinic visit. App patients will receive a download coupon for the app before they leave home and are at liberty to download the app at home to their own devices. The clinic visit usually last approximately 45 min during which the participant can listen to the app or white noise as little or much as he or she desires.

5.2 Handling of Study Interventions

The study site will receive 4 tablets labeled A,B,C,D without knowledge which tablet contains the app and which contains white noise.

5.3 Concomitant Interventions

n/a

5.3.1 Allowed Interventions

n/a

5.3.2 Required Interventions

n/a

5.3.3 Prohibited Interventions

n/a.

5.4 Adherence Assessment

Throughout the project we have and will continue to use the agile approach of Behavior-Driven-Development (BDD) to design and implement features that research suggests to be effective (1)(http://www.bdd-in-action.com/). This has been achieved for the prototype which is functioning according to spec. Design supports data-mining capability of anonymized selection preferences and feedback. Technical performance and good development practices were insured through review of code and test results by qualified software engineers, and the app stores review and approval process.

In accordance with BDD, testing will be continued during the clinical pilot trial to assess technical performance in the hands of patients. App usage patterns in clinic will be established electronically through background capture of usage data and upload to the database server. This data allows analysis of variables such as options chosen, audio segments played and time spent listening to each segment and in total.

A criterion of success will be that 90% of patients in app group listen to app ≥5 min. This will be a summary result based on the cohort of all app patients and not allow identification of individual patients.

6. STUDY PROCEDURES

The schedule of evaluations and events is shown on the following page and listed in the CRF form in Appendix 15.

6.1 Schedule of Evaluations

Appointment / Procedures	Visit 1	After Visit 1 (upon returning diary)
Study Consent/Assent	X	
Demographics	X	
Medical History	X	
Evaluate eligibility and withdrawal criteria	X	
Randomization	X	
NIDA Quick Screen	X	
Pre-Intervention Pain/Anxiety Scales	X	
Tablet Intervention	X	
Intervention Pain/Anxiety Scales	X	
Diary Distribution	X	
Satisfaction Survey	X	
Diary Return (via mail)		X
Check Distribution (via mail)		X
Coupon Distribution (test group)	X	
Coupon Distribution (control group)		X

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

The study team will review the Craniofacial Pain Center schedule to identify patients that are at least 18 years of age with an upcoming visit. Potential subjects will be contacted via phone by a research team member prior to their upcoming visit to introduce the study, using an IRB-approved phone script. If the patient is interested in participating in the study, they will be asked to come into the clinic half an hour before their scheduled appointment. This half hour will be used to consent the participant, and complete randomization.

Patients who present at the Craniofacial Pain Center may also be approached by a member of the research team, and asked for their interest to participate.

All of the forms of recruitment have been submitted to the Tufts IRB and been approved. The screening interview/questionnaire or screening script will be used for recruitment. They do not require separate consent. There will be a single consent form.

The site PI and research assistant will perform the consent procedure.

Patients' level of education will not be an eligibility prerequisite. To be eligible to participate, patients need the cognitive ability, through whichever education acquired, to write and read in English, as the ComfortTalk scripts, study scales and take-home diary are in English and to be able to operate a standard smart tablet or smart phone.

The protocol and consent forms are reviewed on annual basis through the Tufts IRB. Should the need for changes become necessary they will be handled through the Tufts' IRB after prior review by NCCIH.

All study records, including assent forms will be kept in locked cabinets at the Tufts Dental School in a room that has limited access and remains locked at all times. Once the study is terminated, all study records will be kept in locked cabinets or will be sent to Iron Mountain (a contracted secure off site facility) at the end of the study. They will be maintained for a minimum of 7 years.

Data entry quality reports, including availability of signed consent forms, will be prepared by an outside quality monitor every 4 months and submitted to Hypnalegsics, LLC, as described in the DSMP. The first report will be obtained early during the enrollment Phase (month 1-3), and if satisfactory with regard to quality, obtained again 4 months later or after the last patient has been enrolled, whichever occurs earlier. Should there be concerns an earlier follow-up visit will be done.

Screening

There are no specific screening tests or evaluations. Patients will be asked to come 30 min prior to their routine clinic appointment to enable the consent and confirm eligibility criteria:

- Male or female patients age 18 years and older
- Scheduled to undergo a dental procedure at the Craniofacial Pain Center
- Able to hear, write and read in English, as the ComfortTalk scripts, study scales and take-home diary are in English
- Able to operate a standard smart tablet or smart phone and have access to a smart tablet, smart phone at home, or computer-based app download
- Willing and able to give informed consent

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

There is a single informed consent form. Enrollment is defined as the randomization date and is recorded on the case report form.

Baseline Assessments

Once the patient is enrolled ***Demographics*** and ***History*** will be recorded on the Tufts University School of Dental Medicine Research Participant& Dental History form (Appendix).

Assessments include:

- Age
- Gender
- Race
- Medical history
- Medications

Eligibility and withdrawal criteria will be rechecked prior to randomization by going through the CRF form.

The participant will be asked to complete a ***NIDA Quick Screen***. No identifiable information will be collected on the NIDA Quick Screen (only the subject ID number). The NIDA (National Institute on Drug Abuse) Quick Screen will be used to assess drug use (including tobacco, alcohol and illegal substances) and nonmedical use of prescription drugs. The NIDA Quick Screen is a brief questionnaire that addresses overall substance use risk, with likely utility for use in a dental setting. This screening tool is intended to be used by doctors serving adult patients in general medical settings. Its algorithm also identifies patients in need of counseling. The instrument is not used as legal-criminal screen. Furthermore, the NIDA is expected to be a routine tool for the history intake at the Craniofacial Pain Center as an important clinical tool in patient assessment.

The information collected via the NIDA quick screen will be compared to post-visit self-reported medication data from the diary, in order to evaluate any changes in opioid use after their dental visits

The participant will then be verbally asked to indicate his/her ***anxiety and pain levels*** on validated 0-10 scales (0-no pain/anxiety at all, 10-worst pain/anxiety possible). The research assistant will ask about their pain and anxiety using the same verbiage provided on the patient diary, and record their response.

Randomization

Randomization will be performed after completion of screening and baseline to determine which tablet and thereby study intervention the patient will receive.

6.2.3 Blinding

Treating dental personnel will be blinded to group attribution. The treating personnel are the subject's regular scheduled providers, and are not part of the study team. The four tablets used in the study will be labeled A,B,C,D and will be preloaded with the app or white noise by the Hypnalgesics, LLC in randomized sequence. The study personnel at TUSDM will not be aware which tablet presents test or control content. The opening screen and option screen of the white noise control app will use the same color scheme and lay-out as the one of the test Comfort Talk app to minimize the likelihood that personnel become aware of the patient's group attribution. While there may still be a possibility of unblinding in the waiting room or procedure room should the patient ask the research assistant a direct question, strict blinding will be maintained for the analysis for the data. The statistical team of Dr. Finkelman and Ms. Roomian will receive the encoded data entries and will not be informed about the content of the tablets until all analyses are completed. Since they also will not have direct contact with the study patients they are also not at risk of becoming unblinded during app use by the patients.

Patients randomized to the app will receive a download coupon for the app at the time of their visit for home use. Patients attributed to the control group will receive a coupon code after their return their post-visit diary a week later. To enable this while maintaining blinding of study personnel, at the end of their visit, all patients will receive a sealed envelope exteriorly labeled with A,B,C,D according to their group attribution. The Hypnalgesics, LLC will have prefilled and sealed the envelopes according to group attribution either with a download coupon for patients receiving the test tablets, and a thank you note and information that they will receive their download code after they send in their questionnaire for control patients.

All patients sending back their diaries will receive the download coupon with their check. This will lead to some duplication for the test patients who already had received a download coupon at the time of their clinic visit but this will maintain blinding of study personnel.

The study intervention does not carry risks such as drug trial would in that patient management would need be changed based on which group a patient had been

attributed to. Therefore circumstances which would require breaking the bind are not envisioned.

6.2.4 Follow-up Visits

None

6.2.5 Completion/Final Evaluation

The outpatient visit at the time of enrollment is the participant's first and at the same time final visit with regard to the study.

After obtaining the baseline data the research assistant will hand the participant a tablet containing, depending on the group attribution, either the app (App Group) or white noise (Control Group) and will be shown how to operate the tablet.

Participant will then return to the clinic waiting area with the tablet and wait for their regularly scheduled appointment. The patient will be at liberty to when and for how long to listen.

At the end of the waiting room period the participant will be queried again for their levels of pain and anxiety.

After the participant enters the treatment room, he or she will be able to continue to listen to the app or white noise on the tablet. The treating dental practitioner will not be made aware of the group attribution and conduct the treatment as usual. The research assistant will ask the participant every 10 min (+/- 2 minutes) to indicate their pain and anxiety levels. The research assistant will note the duration of chair time, the amount of lidocaine given, if any or which other medications were given during the appointment, and whether the dental practitioner prescribed opioid, prescription or non-prescription drugs at the end of the visit. This information will be obtained by the research assistant from the standard of care provider at the end of treatment.

Before leaving home, the participant will be asked to fill out a satisfaction survey based on a modified Press Ganey Template. The participant will then receive a diary card on which to note pain, average and maximal pain as well its location, use of non-prescription, prescription, and opiate drugs, use of the app, and be provided pre-stamped envelopes. Patients will be asked to complete the diary daily before bedtime for 7 days. Patients in the experimental group will receive a coupon (coded by group) for free download of the app at the end of their study visit.

Once the diary is mailed back and received by the study team, the participant will be sent a check in the mail. Participants randomized to the control condition will also receive a coupon for the app upon returning the diary.

Participants who discontinue the study intervention early do not require any specific evaluation or follow-up. Potential reasons for early termination may be that patient's dental treatment is cancelled by the treating clinician or that the patient doesn't want to be bothered to provide more data. Since this study is on an intent-to-treat all study

data that are already collected will be maintained and the total patient enrollment numbers will form the denominator of analyses.

7. SAFETY ASSESSMENTS

The app is a non-Significant Risk Device (NSR). It does not perform diagnostic tasks or tie in with a device that requires FDA clearance (such as apps aiding in ECG interpretation or detection of skin malignancies). The NSR status was confirmed by the Tufts IRB approval letter of 7/20/2017.

7.1 Specification of Safety Parameters

Expected risks to the subject are as follows:

The risks of participating in this study are not beyond the normal risks for the dental procedures in the TUSDM Craniofacial Pain Center which are considered standard of care.

Patients who are randomized to one of the control group and who are anxious may be disappointed for not getting the app while waiting.

There is the risk of loss of confidentiality to the subject by participating in this study. This risk will be kept to a minimum by following procedures listed under the confidentiality section of the TUSDM IRB.

These risks are considered to be minimal and are addressed in the protocol and consent form.

Because any dental procedure with or without the app can cause increasing anxiety and pain, anxiety and pain will be monitored at frequent intervals with validated 0-10 verbal assessment scales during their clinic visit. The investigators at the Craniofacial Pain Center at TUSDM are furthermore experts in managing patient's pain and distress and assure (as they do for all their patients) that they leave with acceptable comfort levels. Dr. Kulich and Jackson are furthermore psychologically trained and will be able to recognize any unexpected AEs related to participating in the study.

When patients hear drill sounds or had prior traumatic experiences and the environment suddenly reminds them of those, they can vividly relieve the old trauma. This is very rare in a dental setting and can occur whether patients would listen to an app or not.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Adverse events will be recorded in source documents and on case report forms. All adverse events and non-serious situations will be recorded, monitored, and reported to the IRB at time of continuing review or at the study's termination if this occurs before the study's next continuing review.

To assess relationship of an event to study intervention, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    i. The event is known to occur with the study intervention.
    ii. There is a temporal relationship between the intervention and event onset.
    iii. The event abates when the intervention is discontinued.
    iv. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    i. There is no temporal relationship between the intervention and event onset.
    ii. An alternate etiology has been established.

7.3 Adverse Events and Serious Adverse Events

Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a human subject, including any abnormal physical exam or laboratory finding, symptom, or disease, temporally associated with a subject's participation in the research.

Unanticipated Problems (UP)

An unanticipated problem is an incident, experience, or outcome that meets all of the following criteria: 1) The nature, severity, or frequency is unexpected for the subject population or research activities as described in the current IRB approved protocol, supporting documents, and the ICF(s); 2) it is related or possibly related to participation in the research; 3) it suggests the research may place the subject or others at a greater risk of harm then was previously recognized.

Unanticipated Adverse Device Effects (UADEs)

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Serious Adverse Event (SAE)
A serious adverse event is one that results in death, or is life-threatening, or results in hospitalization or prolongation of existing hospitalization, or results in a persistent or significant disability/incapacitation, or results in a congenital anomaly/birth defect, or may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above.

7.4 Reporting Procedures

Adverse events will be recorded in source documents and on case report forms. All adverse events and non-serious situations will be recorded, monitored, and reported to the IRB at time of continuing review or at the study's termination if this occurs before the study's next continuing review.

Serious adverse events will be recorded in source documents and on case report forms. Serious Adverse Events that meet the criteria of an unanticipated problem will be reported to the IRB within 5 business days following the Reportable New Information Policy. Serious Adverse Events not meeting the criteria for an unanticipated problem will be reported to the IRB at time of continuing review or at the study's termination if this occurs before the study's next continuing review.

Unanticipated problems will be recorded in source documents and on case report forms. Unanticipated problems will be reported to the IRB within 5 business days after the PI/study team becomes aware of the problem. A Reportable New Information Form will be submitted to the IRB no later than 5 business days after the PI/study team becomes aware of the problem.

UADEs will be documented in source documents and on case report forms as to onset, severity, duration, management, outcome and relatedness to the test device. UADEs will be reported to the IRB within 5 business days after learning of the effect.

7.5 Follow-up for Adverse Events

AEs will be followed until resolved or considered stable through the psychologists of the Craniofacial treatment Center at Tufts (Drs. Kulich, the site PI, and Dr. Jackson, the research assistant).

7.6 Safety Monitoring

A Data Safety Monitoring Plan (DSMP) and Independent Monitoring Committee protocol has been submitted to NCCIH on 06/01/2017 and has been approved.

8. INTERVENTION DISCONTINUATION

Subject Withdrawal/Termination Criteria are

- Subjects who do not comply with the study procedures, such as not returning diaries
- Subjects who decide to stop participating in the study will be withdrawn from further data requests.

The Site-Principal Investigator and clinical co-investigators will determine whether subjects (either withdrawn subjects or subjects completing the study) are in need of additional treatment and/or follow-up observation as a result of participation in this trial. Subjects and/or their insurance will be responsible for the cost of any standard of care follow-up visits or additional treatment that is not part of this study.

If a subject withdraws or is withdrawn, any data collected up to that point will still be used for the study which is on an Intent-to-Treat basis and therefore will include the withdrawn individuals in the denominator. However, no further data will be collected for that subject.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This randomized controlled trial is a single-site pilot trial to assist in feasibility assessment and sample size estimation in a pivotal trial to test the hypothesis that listening to a Comfort Talk® app with calmative content reduces pain, anxiety, and post-procedural medication use. The study design is based on a 1:1 randomized attribution of participants to an app or white noise as control condition.

The feasibility criteria are not hypothesis driven and are based on practical pass/fail criteria:

primary feasibility outcome parameter:

- ability to obtain complete on-site data sets from at least 90% of patients enrolled - with at least 40% from patients in the app group and at least 40% from patients in the control group)

secondary feasibility outcome parameters:

- ability to enroll 60 patients by day 150 after initiation of recruitment in the clinic (=day 1)
- obtaining 38 packages of filled out diary cards (at least 16 from patients in the app group and at least 16 from patients in the control group).
- 90% of patients in app group listen to app ≥5 min

Since a significant reduction in anxiety in the waiting room is the main ingredient that underlies all other hypothesized effects for Phase II outcomes, even in the face of proven technical feasibility of trial execution, it was chosen as the overall primary objective for Phase II.

Statistical hypotheses for Phase II are:

Providing participants a calmative Comfort Talk® app at the time of their dental outpatient visit

- reduces anxiety in the dental waiting room (primary hypothesis)
- reduces pain in the dental waiting room
- reduces anxiety during dental treatment
- reduces pain during dental treatment
- improves patient satisfaction with the dental visit
- reduces anxiety in the week after treatment
- reduces pain in the week after treatment
- reduces need for opioids and analgesics the week after treatment

The overall premise is that showing patients at the time they experience distress how to cope while they are still under physician/dentist supervision will carry over into recovery and thus reduce need for addictive drugs (see also 2.2).

9.2 Sample Size and Randomization

The goal is to enroll 72 patients in a randomized design with 36 patients utilizing the app and 36 patients not utilizing the app. Those randomized to utilizing the app (app group) will receive a tablet with the app, those randomized to not utilizing the app (control group) will receive a tablet with white noise.

Based on prior trial experience, it is likely that 90% of patients on site will provide onsite data sets (primary objective). In two prior trials, in which 241 and 201 patients, respectively, were followed through their invasive medical procedures, all enrolled patients (100%) provided these data (1,3). In a breast-biopsy trial, 4 of 240 (1.6%) withdrew by that stage (2). In these past trials patients received more personal attention through live delivery of the content that is now offered in an app, and thus willingness to remain in the study may not be as high in the current trial but still should exceed 90% for feasibility. To arrive at a reasonable sample size to satisfy this requirement, but also obtain a sense of validity of the primary hypothesis for Phase II and obtain estimates of data distribution, which will be critical for sample size and analysis planning Phase II, we conducted following sample size calculations.

Assuming an average anxiety rating of 4 at the end of the waiting room time without prior guidance in relaxation or app (see Fig 3., time 0), the expectation of improved subsequent outcomes with a 35% reduction in anxiety to 2.6 based on Schupp et al (33 vs 53 on STAI - (1) and a standard deviation of 2, 66 patients would be needed for a two-sided test with a power of 0.80 and an alpha of 0.05.

This degree of reduction in anxiety is clinically significant based on prior work in a clinical trial that demonstrated that a 35% difference in anxiety at the onset of an invasive medical procedure is associated with significant differences in the subsequent experience of pain and anxiety during the procedure, need for opioid analgesics and sedatives, and the overall length of the procedure. These factors directly affect procedure safety and throughput (e.g. economical efficiency).

Using this number of 66 patients as guide to determine a target study size for assessment of the feasibility parameters an enrollment of 72 patients seemed compatible with an early drop-out of 6 patients resulting in an expected 91.7% onsite data return rate. This will also support the expectation of receiving 38 packages of filled out diary cards (53%), a secondary objective. In a prior breast biopsy trial, in which patients collected for 5 days 4 daily salivary cortisol samples, filled out more extensive diary cards, and sent all back to the lab, 36% complied (45). Considering the higher burden of also getting 4 daily salivary samples and 4 daily entries as compared to one daily entry on cards at bed-time a 53% return rate for this pilot is reasonable.

This sample size of 72 participants may also give an estimate in as far results previously achieved with live delivery of Comfort Talk® may be transferable to assumptions for app delivered Comfort Talk® content.

The following sample size estimate supports the evaluation of post-procedure pain and is based on a prior breast biopsy trial (19) during which we collected postoperative pain measures. In that study, postoperative pain ratings in the live Comfort Talk group were less than those of the control group (1.6 vs 3.5) with a standard deviation of 2.0. Assuming a similar reduction in pain from 3.5 to 1.6 on day 1 (similar effect size in a study by from TUSDM) (43) and a standard deviation of 2.0, 38 subjects total would be needed for a two-sided test with a power of 0.80 and an alpha of 0.05. Considering that not everyone will send back their diaries, the target of 72 patients may suffice.

Treatment Assignment Procedures

Randomization was chosen as it provides the highest level of scientific evidence.

This is a pilot trial with a relatively small number of participants. The randomization codes will not be broken until all statistical analyses having been performed by the statisticians in a blinded fashion.

We will use 4 tablets, 2 with Comfort Talk content, two with white noise, labeled A,B,C,D. The tablets will be preloaded with the respective app content in a randomized sequence at Hypnalgesics, unknown to the Tufts investigators.

Dr. Jackson/research assistant will consent the patients, hand the patient the tablet based on the randomization scheme (which will be provided by Drs. Finkelman and Roomian), obtain baseline data, query and record trial data but **will not analyze** data. There is a possibility that he may become unblinded, however he will not share his observations with the analyzing team.

Strict blinding will be maintained for the analyzing team. Analysis of data will be performed by the statisticians Drs. Finkelman and Roomian, who will remain blinded throughout the trial as to which tablet contained which content. They will not have any patient interactions and thus also will also not be privy to any accidental unblinding of tablet content during the dental treatment.

9.3 Definition of Populations

The study is based on ITT (Intent to treat).

9.4 Interim Analyses and Stopping Rules

There is no plan for interim analyses.

This study may be terminated for the following reasons:

- Discovery of unforeseen risk that could jeopardize the dental/physical well-being of subjects.
- Enrollment or recall rates that are not likely to produce sufficient data for evaluation of safety and efficacy
- Non-compliance with the clinical investigational plan, the Investigator
- Agreement, applicable FDA regulations or conditions of approval imposed by the reviewing IRB
- Any new information becomes available during the trial that necessitates stopping the trial
- Withdrawal of IRB approval

Findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events. Such findings are presented to the Independent Monitoring Committee (IMC) statistician to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician reports his findings to a closed session of the IMC or to the Safety Officer and/or NCCIH. The findings are used to determine what steps will be taken.

9.5 Outcomes

The outcomes are based on patient's reported measures of anxiety, pain, satisfaction rating on a Likert scale, and medication use and objective numbers with regard to the feasibility measures. These data are clear numerical values and not subject to interpretation/adjudication with regard to their reported value.

There will be no loss of follow-up for data for the primary outcome parameter since all patients who are on site are the denominator and any missing data would be reflected in the percentage of complete on-site data sets.

For management of any subsequent missing intermittent data the method will use all data available data that are available within the intent-to-treat overall approach.

We will be using all available data and calculate the percent missing data for each treatment group. The degree of missingness will inform accept/reject feasibility which is defined as complete on-site data sets from at least 90% of patients enrolled with at least 40% from patients in the app group and at least 40% from patients in the control group) and 38 packages of filled out diary cards 52% with at least 16 (22%) from patients in the app group and at least 16 from patients in the control group (22%)

9.5.1 Primary Outcome

- percentage of complete on-site data sets

9.5.2 Secondary Outcomes

With regard to Phase I of the trial feasibility parameters will be

- number of enrolled patients by day 150 after initiation of recruitment in the clinic (=day 1)
- number of returned packages of filled out diary cards.
- percentage of patients in app group listen to app ≥5 min

With regard to Phase I

- anxiety on a validated 0-10 scale in the dental waiting room
- pain on a validated 0-10 scale in the dental waiting room
- anxiety q10 min (+/- 2 mins) on during dental treatment
- pain q10 min (+/- 2 mins) during dental treatment
- anxiety, average, and maximal anxiety for 7 days after treatment
- pain, average and maximal pain for 7 days after treatment
- use of prescription and nonprescription drugs for 7 days after treatment
- patient satisfaction
-

Pain and anxiety will be measured on 0-10 verbal self-reporting scales (0=no pain/anxiety at all, and 10=worst pain possible). The pain scale is recommended standard in the NIH Toolbox (62). For the 0-10 anxiety scale we previously demonstrated convergent and discriminant validity (63).

Anxiety and pain measures will obtained using these scales by verbally asking the patient “How is your Comfort Level on a scale with 0-no anxiety at all, and 10 worst anxiety possible and 0=no pain at all and 10=worst pain possible”:

- At the beginning of the waiting room time after consent
- At the end of the waiting room time
- After the patient enters the dental treatment room and sits down = time 0 of chair time
- Every 10 minutes (+/- 2 minutes) thereafter while on the chair
- When leaving the dental treatment room

Once returned home the patients are asked to use the same scales to write down on daily diary cards for 7 days before bedtime as follows:

PLEASE INDICATE YOUR COMFORT LEVELS WITH A NUMBER BETWEEN 0 and 10

With regard to pain (0=no pain at all and 10=worst pain possible)

- Right now:
- On the average today:
- At its maximum today:

With regard to anxiety (0=no anxiety at all and 10=worst anxiety possible)

- Right now:
- On the average today:
- At its maximum today:

Patient Satisfaction will be assessed using a modified Press Ganey Outpatient Survey template *(64)* adjusted to dental care and supplemented with a question regarding helpfulness of the app on the same 5-point scale as the remainder of the survey. The Press Ganey instrument has been found to possess suitable psychometric properties for outpatient medical practice survey (65).

9.6 Data Analyses

All outcome parameters for assessment of study feasibility are pass/fail criteria not requiring further analyses beyond calculations of sums and percentages.

To commit to a detailed analyses in Phase II, this can only be done with the proviso that the approach may change based on the data distribution, central measures and variation, and particularly time course, the determination of which is a goal of this Phase I trial.

For comparison of change in anxiety and pain from start to end of the waiting room time we propose t-test if normally distributed or the Mann-Whitney U test in the case of non-normal data.

For the time course assessment of pain and anxiety during the procedure there are options depending on whether the data meet the assumptions required for time course analysis.

Descriptive statistics (means and standard deviations as well as counts and percentages) will be calculated for each outcome stratified by time point and by

treatment group. Pain and anxiety trends over time will be assessed graphically for each patient stratified by treatment group.

With the provision that the analysis plan will be adapted based on the metrics found in Phase I, the plan is to follow a previously described path (24):

If the relationship between pain/anxiety is linear over time, and if needed, normality and homoscedasticity of residuals can be achieved by log-transformation, a repeated-measures analysis to compare the effect of treatment, time, and treatment by time interaction on pain and anxiety responses to characterize and compare trends in pain and anxiety ratings for the two treatment conditions over time (66, 67).The analysis will use the reports from the successive 10 min (+/- 2 mins) intervals queries obtained from all patients.

It may be that residuals are neither normally distributed nor possible to obtain a normal distribution by transformation. This happened in prior large scale trial with procedural pain procedural were 47% of pain responses were zero (45). To accommodate such a strong skew in reported pain, we would change our statistical approach to ordinal regression (68). If the proportional odds assumption is met, ordinal regression accounting for repeated measures will be performed to compare the effect of treatment, time, and interaction of treatment by time on pain and anxiety responses. The results will be presented in terms of the slopes of the time course of pain and anxiety on the logit scale.

If the data does not meet the assumptions required for the time-series analysis methods listed above, the time-series data from each patient will be summarized by calculating area under the curve using trapezoidal rule. Normality will be assessed graphically using histograms and q-q plots. Area under the curve will be compared between the two treatment groups using t-test if normally distributed or if normality can be achieved by log-transformation. Mann-Whitney U test will be used if data is non-normal.

Pain and anxiety for the week after the post procedure will be assessed for linearity graphically. Individual patient pain and anxiety slopes will be compared using t-test or Mann-Whitney U test, as appropriate, to determine if the rate of change of pain and anxiety is different between treatment and control groups. In addition, the overall mean pain and mean anxiety for each patient will be calculated and compared between treatment and control groups using t-test or Mann-Whitney U test as appropriate.

Drug usage, converted in equivalence drug score, and satisfaction scores will be assessed by t-test if normally distributed or Mann-Whitney-U test if non-normal.

All tests will be two-sided at a significance level of <0.05. Sample size will be based on results of Phase I assuming a power of 80%. SAS version 9.4 will be used for analysis.

Patients' age, gender, procedure type, and NIDA Quick score will be assessed for their potential as confounding factors. This will support guidance for trial design in Phase II.

The study sample of this pilot is likely underpowered to perform meaningful sub-analyses of differences in intervention effect between gender and racial/ethnic subgroups. They will be performed to not miss potentially clinically significant differences as prescribed by NIH policy.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

The research assistant will fill out the data collection forms.

10.2 Data Management

The site Principal investigator will maintain all study records and documents during the study period. All paper files and documents will be kept in a locked file cabinet, within a locked room at the Tufts Craniofacial Pain Center, 6th Floor, TUSDM). Electronic records will be kept on a password-protected computer.

There is no Coordinating Center in this single-site trial and statistical data evaluation will be performed by the Tufts Statistical Department's site co-investigators Drs. Finkelmann and Roomian.

Data collection forms are attached in the Appendix and include demographics, medical history, adherence to protocol, baseline and outcome data.

10.3 Quality Assurance

10.3.1 Training

All study staff are trained and certified on procedures specific to their role. Study team member CV's, noting all completing training, will be stored in the Regulatory Binder.

All study staff involved in study (listed in Personnel) will be trained on the Good Clinical Practice Guidelines (GCP) as outlined in the Guidance for Industry E6 Good Clinical Practice Consolidated Guideline and in accordance with the FDA Code of Federal Regulations Title 21 part 50 Food & Drugs Administration. GCP principles are not protocol specific, but rather apply to any type of clinical trial.

All study staff at Tufts are required to complete the Research Administration GCP Tutorial Program located in the "Research Coordinator Training" binder and pass the corresponding quiz. Record of completion will be kept on site.

IRB requires all researchers (investigators, assistants, coordinators, etc.) conducting human subject research to complete the necessary requirements, as outlined by the IRB, on an annual basis. All study staff at Tufts are required to complete HIPAA training and CITI training via the following website: *https://www.citiprogram.org*

10.3.2 Quality Control Committee

All subject records, including consent documentation, CRFs, and source documents are reviewed by study staff internally. Records are reviewed by at least one coordinator after each subject visit and then reviewed again by another study staff member for accuracy.

In addition, an outside monitor (Dr. C. Kusnick. CMO, Clinical, Medical, and Regulatory Affairs of Headlands, Inc) will review the study files every 4 months during the time of patient enrollment and verify Case Report Form data against source documents. For this purpose, Dr. Kusnick will review a sample of 30% of study documents.

Study records are also subject to review/monitoring at any time by the IRB, Hypnalgesics, LLC, or other governing agency such as the FDA. A record of all outside monitoring visits should be kept in the Regulatory Binder.

10.3.3 Metrics

Quality control measures include routine inspection of case report forms, source documents, data tabulations, and tracking of adverse events. Quality will be based on adherence to the protocol and congruence of the electronic summary data and the source data. The outside monitor will assure that 100% of patients are real. Internal staff and the outside monitor will further note that patients were appropriately consented, that all data were collected, and endpoints recorded correctly. Minor and infrequent transcription errors are easily corrected. Major and/or systemic deviations would be addressed by retraining and reported to IRB and NCCIH.

10.3.4 Protocol Deviations

It may not be possible to avoid all protocol deviations, but they will be logged and reported. Protocol deviations will be captured and documented in the source documents. They will be reviewed by the Site PI, Internal QA reviewer, Hypnalgesics, LLC and independent monitor.

No protocol changes will be made without prior agreement by the IRB and Hypnalgesics unless implemented to prevent an immediate hazard to subjects. All other protocol changes or deviations will be made by a formal amendment subject to IRB approval. All such changes or deviations will be reported to the IRB and NCCIH as they occur and included in the final study report. Significant protocol changes require NCCIH review and approval before submission to the IRB.

10.3.5 Monitoring

Monitoring is summarized in Table 2:

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PI, Internal QA Reviewer, Hypnalgesics, LLC
	Semi-annually	Independent Monitor(s)
Status of all enrolled subjects, as of date of reporting	Monthly	PI, Internal QA Reviewer, Hypnalgesics, LLC
	Semi-annually	Independent Monitor(s)
Data entry quality control checks on 30% of charts	Every 4 Months	Outside QA-CRP Reviewer
Adherence data regarding study visits and intervention	Monthly	PI, Internal QA Reviewer, Hypnalgesics, LLC
	Semi-annually	Independent Monitor(s)
AEs	Monthly	PI, Internal QA Reviewer, Hypnalgesics, LLC
	Semi-annually	Independent Monitor(s)
	Annually	NCCIH, IRB
SAEs (unexpected and related)	Per occurrence	PI, Independent Monitor(s,) Hypnalgesics, LLC, NIH/NCCIH
	Per Policy	IRB
SAEs (expected or unrelated)	Per Occurrence	PI, Internal QA Reviewer, Hypnalgesics, LLC
	Annually	Independent Monitor (s), NIH/NCCIH, IRB
Unanticipated Problems	Monthly	PI, Internal QA Reviewer. Hypnalgesics, LLC
	Per Policy	IRB

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

The Tufts IRB has reviewed and approved the study protocol and the informed consent documents in the Appendix. Any subsequent modifications will be reviewed and approved by NCCIH and the IRB.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant as described in 4.3. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

The participants will be asked to read the informed consent form (ICF). Subjects will be given ample time to have any questions answered. If a subject decides to participate, he or she will be asked to sign the ICF as applicable. A copy of all consent documents will be given to the subject.
This fact will be documented in the participant's record.

11.3 Participant Confidentiality

To ensure confidentiality of subject information, each subject enrolled in the study will be assigned a unique alphanumeric code. Subjects' files will be kept in a secure, locked cabinet in a secure room at the Tufts Craniofacial Pain Center, 6th Floor, TUSDM when the files are not being reviewed. The information will only be shared between the researchers. All HIPAA requirements will be followed. All electronic files will be kept on a password protected computer in a secure, locked office.

Choice of app segments and length of playing will be derived from anonymized tablet information used by participants at the clinic. App usage during the study visit will not be linked to the individual participant's subject ID. To ensure patient confidentiality downloads to the patients' own devices will not be traceable to the patient as implemented by Apple store policies.

Study compensation will be provided by check. In order to issue a check, participants will be asked to fill out a check voucher form and complete a W-9 tax form. Once the diary is returned, this paperwork will be used to process and send a check to the participant via mail. This paperwork will be stored with the subject file in a secure, locked cabinet in a secure room throughout the duration of the study. Upon study completion, the documents may be shipped to Iron Mountain for long term storage.

(a) Coding
Each will be assigned a subject identification number. Alphanumeric identification numbers will be assigned sequentially. The full subject identification number will consist of the three letters from the subject's initials and their enrollment number. This will be accessible by study personnel only.

(b) Access

Only study personnel will have access to data. Investigators will permit monitoring, audits, and regulatory inspections and will provide direct access to study related documentation.

Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NCCIH, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

n/a

13. PUBLICATION OF RESEARCH FINDINGS

The investigators are free to publish their findings. There is no Steering Committee.

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15. SUPPLEMENTS/APPENDICES

CRF documents
Medical/Dental History Template
NIDA Quick Screen
Satisfaction Survey
Daily Pain/Anxiety Diary
Tufts IRB Protocol approval letter incl. consent form