EMPOWER:

Evaluating the ability to reduce Morphine equivalent dose for chronic Pain patients receiving Opioid-therapy through a Web-based E-Health self-management program: a Randomized multi-site clinical trial in primary care

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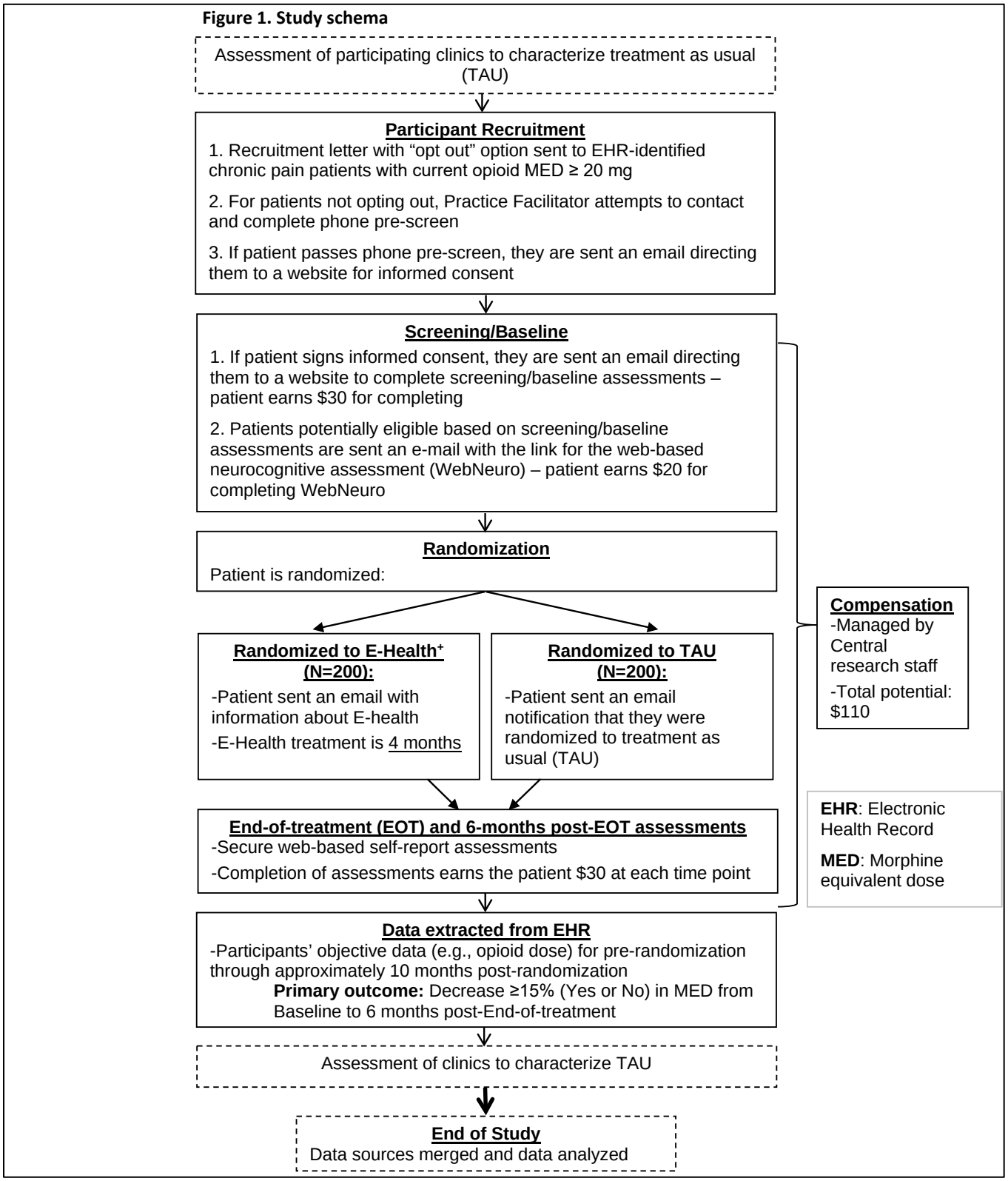
Table of Contents

1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACIC	Assessment of Chronic Illness Care
AE	Adverse Event
BPI	Brief Pain Inventory
COMM	Current Opioid Misuse Measure
CPMP	Chronic Pain Management Program
CRF	Case report form
CSQ-R	Coping Strategy Questionnaire-Revised
DASS-21	Depression, Anxiety, and Stress Scales
DSMB	Data and Safety Monitoring Board
EHR	Electronic Health Record
EOT	End of Treatment
IRB	Institutional review board
ITT	Intent-to-Treat
LOT	Long-term opioid therapy
MED	Morphine Equivalent Dose
NIDA	National Institute on Drug Abuse
PF	Practice Facilitator
PI	Principal Investigator
PROMIS	Patient-Reported Outcomes Measurement Information System
PSEQ	Pain Self-Efficacy Questionnaire
SAE	Serious Adverse Event
RA	Research assistant
RCT	Randomized controlled trials
TAU	Treatment as Usual
TMT-B	Trail Making Test B

2.0 STUDY SCHEMA

Figure 1: Study Schema



3.0 STUDY SYNOPSIS

STUDY OBJECTIVES. The primary objective of this study is to evaluate the impact of treatment as usual (TAU), relative to TAU plus access to a web-based chronic pain program (E-health$^+$), in patients with chronic non-cancer pain being treated with long-term opioid therapy (LOT). It is hypothesized that the E-health$^+$, relative to TAU, group will have a significantly greater proportion of participants with a: 1) ≥15% reduction in daily morphine equivalent dose (MED) as assessed by the EHR (H_1: primary), and 2) clinically significant decrease (i.e. ≥ 2 points) in Pain Intensity score as measured by the Brief Pain Inventory (H_2: key secondary) at 6 months post-treatment.

STUDY DESIGN. This is a 10-month, intent-to-treat, 2-group randomized controlled trial. Eligible participants will be randomized to TAU or E-Health$^+$, stratified by site. Participants will be assessed at baseline, at the end of the 4-month treatment period, and at 6 months following end-of-treatment through an electronic data capture system accessed by the participants. Other outcome data will be obtained from the participant's electronic health record (EHR).

STUDY POPULATION. Approximately 400 participants, recruited from primary care and pain management practices within one of two healthcare systems (University of Cincinnati Health and Duke Health), will be randomized into the study. Each healthcare system will randomize approximately 200 participants. The study population will include individuals who are 25-80 years of age, being treated with LOT (≥3 months) for chronic pain with a MED ≥ 20 mg, and who have internet access.

TREATMENTS. Participants randomized to TAU will receive treatment for chronic pain as typically provided by their clinician. Participants randomized to the E-health$^+$ arm will receive treatment as typically provided by their clinician plus a 4-month subscription to an internet based chronic pain program (the Chronic Pain Management Program from Goalistics).

ASSESSMENTS. Data to calculate MED will be derived from the participant's EHR. The Brief Pain Inventory and other patient-reported assessments will be collected on-line using REDCap.

PRIMARY ANALYSIS. The primary hypothesis is that a significantly greater proportion of E-health$^+$, relative to TAU, participants will have a ≥15% decrease in MED between baseline and 10-month (i.e., 6-month post-treatment) follow-up. The MED outcome may be prone to site effects in that the strategies used by the healthcare system to treat chronic pain may influence prescribing behavior; thus, the primary analysis will test for potential site (UC Health vs. Duke) effects. Specifically, a logistic regression will test for treatment (E-health$^+$ vs. TAU), site, and treatment-by-site interaction effects, with treatment being the effect of interest.

4.0 BACKGROUND AND SIGNIFICANCE

An estimated 100 million Americans suffer from **chronic non-cancer pain** (**referred to as chronic pain**). The treatment of chronic non-cancer pain has largely fallen to physicians who often, due to healthcare system constraints, rely exclusively on long-term opioid therapy (LOT).[1, 2] Gaps in policy, treatment, education and research have resulted in shortfalls in pain care and unintended deaths from opioids.[3] In 2012, 259 million opioid prescriptions were written by U.S. health care providers -- enough for every adult to have a prescription. This trend has been blamed for the rise in opioid misuse and accidental overdose deaths.[4] Nearly 46 Americans die from an overdose of prescription painkillers each day.[5] A majority (60%) of the more than 15,000 annual opioid analgesic/painkiller overdose deaths in the U.S. occur in patients obtaining prescriptions within medical board prescribing guidelines.[6] It has been estimated that opioid misuse behaviors occur in 1 of every 4 patients receiving opioids for chronic pain and addiction presents in 1 of every 10.[7] Based on the adverse consequences of, and inadequate evidence of effectiveness for, LOT, the CDC recently developed recommendations designed to decrease the use of LOT and the morphine equivalent dose (MED) for patients receiving LOT.[8] However, the majority of people receiving LOT report that opioid medication is significantly beneficial and even critical to managing their pain;[9-11] thus, these patients may be resistant to having their medication reduced or discontinued.[9] This discrepancy between the goal of many policy makers and providers to reduce or discontinue opioid medication for chronic pain treatment and the goal of patients to effectively manage their pain which, in their view, includes the use of opioid medication, will likely result in poor outcomes should opioid reduction be attempted in the absence of accessible, effective non-opioid medication treatment. Indeed, the importance of testing adjunctive therapies to reduce MED was noted in NIDA's new strategic plan.[12]

Due, in part, to the mounting adverse consequences associated with using LOT as the principal treatment for chronic pain, the question of whether there are viable alternative treatments has been asked frequently during the past few years, including by the Institute of Medicine[1] and National Institutes of Health.[2] In order to be viable, the treatment needs to be accessible – both in terms of availability and affordability – and effective. Unfortunately, many potential treatment alternatives, including effective multidisciplinary or interprofessional treatments, are associated with significant barriers, including limited availability in many areas, lack of coverage by many insurance plans, limited patient acceptance, and other limitations.[13-15] Novel treatment approaches are needed to extend access to effective pain care. Self-management programs, which are designed to assist patients in mastering the tasks needed to live with a chronic condition, are promising in this regard. Based on concepts of self-efficacy, they aim to increase a person's confidence and ability to exert control over troubling health symptoms. Self-management programs have been touted as an effective means to improve quality of life and health functioning while reducing health care resource utilization.[16, 17] Pain self-management interventions are recommended as an essential component of evidence-based clinical practice for chronic pain.[18, 19] Online and face-to-face group self-management interventions have demonstrated improved outcomes in small, specific populations of patients who suffer with pain such as patients with fibromyalgia, headaches, arthritis and angina.[17, 20, 21] However, no such interventions have been accepted for widespread use in the general population of patients with chronic pain, and no consensus exists on the optimal means to engage patients in pain self-management strategies. Web-based interventions have the advantage of being more accessible than face-to-face interventions and these two treatment modalities have been found to have equivalent efficacy.[22]

While there is evidence that web-based interventions can be effective for chronic pain, the majority of studies have failed to evaluate their impact on reducing reliance on LOT,[23] with the exception of research on the Chronic Pain Management Program (referred to as E-health), which has been found to be efficacious in decreasing pain and medication use in two prior randomized controlled trials (RCTs). Of critical import, the E-health intervention is particularly well-suited to address the sometimes discrepant goals of policy makers/ providers to reduce LOT and of patients to manage their pain, which, for them, includes LOT. Specifically, two

prior RCTs have found that the E-health program significantly decreased the use of prescription pain medications even though a desire to decrease dose was not an eligibility criterion nor were participants instructed to attempt a dose decrease. In an RCT, conducted with a sample of chronic pain patients heterogeneous for LOT use (N=305), E-health participants reported significantly greater decreases in prescription medication use compared to a wait-list control group.[24] The second RCT, conducted with 92 people with chronic pain with a current opioid prescription found that, E-health, relative to wait-list control, participants evidenced significantly greater decreases in opioid misuse and a significantly greater proportion of E-health participants reported decreasing or discontinuing their opioid medication (21% vs. 7%).[25]

In addition, the E-health participants experienced decreases in pain despite significant decreases in prescription medication use. In the RCT conducted with 305 chronic pain patients, participants randomized to the E-health intervention reported significantly greater decreases in pain severity, pain-related interference and emotional burden, perceived disability, catastrophizing, and pain-induced fear.[26] The second RCT, conducted with 92 people with chronic pain with a current opioid prescription found that 18% of E-health participants, compared to 6% of wait-list control, had a clinically significant decrease (i.e. ≥ 2 points) in Brief Pain Inventory Pain Intensity.[25]

While these results are promising, they need to be replicated in a larger RCT and with patients from primary care and pain management clinics, where the majority of chronic pain patients are treated. In addition to identifying an effective intervention, it is important to identify therapeutic mediators and moderators which would allow for tailored interventions and delineation of therapeutic targets; such evaluation for E-health has been suboptimal due to the constraints of the small sample size of the pilot trial (N=92) and, in the first RCT (N=305), only data on prescription medication, rather than on opioid medication specifically, being collected.

5.0 SPECIFIC AIMS

Aim 1: The primary aim is to evaluate the impact of treatment as usual relative to treatment as usual plus access to a web-based chronic pain program, the Chronic Pain Management Program (E-health^{+}), on daily MED in patients with chronic non-cancer pain being treated with LOT. It is hypothesized that the E-health^{+}, relative to TAU, group will have a significantly greater proportion of participants with a: 1) ≥15% reduction in daily morphine equivalent dose (MED) as assessed by the EHR (H_1: primary), and 2) clinically significant decrease (i.e. ≥ 2 points) in Pain Intensity score as measured by the Brief Pain Inventory (H_2: key secondary) at 6 months post-treatment.

Aim 2: Test our conceptual model of E-health's mechanisms of change, including hypothesized mediators (i.e., pain self-efficacy, coping strategies, knowledge about pain/opioid therapy, and stress) and moderators (neurocognitive function: executive function and verbal learning ability) of E-health's impact on decreasing MED and pain intensity. Moderated mediation analyses will be used to test our conceptual model.

Our study will determine whether an innovative, accessible E-health intervention can assist with reduced opioid reliance in chronic pain patients, which can, ultimately, reduce risks of unintended opioid overdose and death. Importantly, we will better understand the mechanisms contributing to MED reduction while managing pain. Our findings may assist in developing treatment options for a population at risk for opioid adverse effects.

6.0 STUDY DESIGN

6.1 Overview of Study Design

The study schema is provided in **Figure 1**. This is a 10-month, intent-to-treat, 2-group randomized controlled trial. We will randomize 400 participants, recruited from primary care and pain management practices within one of two healthcare systems, in a 1:1 ratio to treatment as usual (TAU) or E-health plus TAU (E-Health^{+}). Participants will be assessed at baseline, at the end of the 4-month treatment period, and at 6 months following end-of-treatment through an electronic data capture system accessed by the participants.

It is possible that the standard practice at the participating sites will change during the course of the trial and, thus, an assessment of the clinics will be completed prior to the start of patient recruitment and after the end of data collection (see **Figure 1**); this will provide more accurate information about the study sites and, thus, about the sites to which the results are most likely to be generalizable. This is a particularly important consideration for this trial in that recent years have seen a significant increase in efforts to improve LOT prescribing practices. These include the CDC guidelines[8] and the recommendation by an FDA Advisory Panel that Risk Evaluation and Mitigation Strategy training be made mandatory for all opioid prescribers.

6.2 Number of Sites and Participants

The two healthcare systems selected for this trial, University of Cincinnati (UC) Health and Duke, have successfully participated in primary care and chronic pain research and have a sufficient pool of potential participants to support this trial. Each health system will randomize approximately 200 participants (for a total N=400), with a target rate of approximately 5.1/month for 39 months.

6.3 Study Duration

An individual participant's period of time for participation and study completion is approximately 11 months. This project will be completed over the course of approximately 5 years.

6.4 Participant Selection

6.4.1 Inclusion Criteria

Potential participants must:

1. be 25-80 years of age
2. be able to understand the study, and having understood, provide informed consent in English
3. have a daily average prescribed MED ≥ 20 mg over a recent three-month period
4. have a chronic pain-related diagnosis
5. self-report current use of opioid medication(s) to treat pain
6. have a Brief Pain Inventory Pain Intensity score ≥3
7. have internet access and a working email account

6.4.2 Exclusion Criteria

Potential participants must not:

1. be anyone who, in the judgment of study staff, would be unlikely to complete the study (e.g., planning to change to a different clinic for pain management, have a terminal illness, etc.)

2. be unwilling/unable to complete the WebNeuro assessments

3. be pregnant

4. be a prisoner

6.5 Outcome Measures

6.5.1 Primary Outcome Measure

The primary outcome measure is whether (yes/no) there was a ≥15% decrease in MED, based on the opioid prescribing information in the participant's EHR, between baseline and 6-month post-treatment follow-up. There is no universally agreed upon method of calculating MED, which can result in inconsistent conversions among clinicians.[27] For the proposed trial, the calculation of MED will use the Opioid Morphine Equivalent Conversion Factors table created by the CDC.[28] There is also no standard definition for what constitutes a significant decrease in MED but a ≥15% decrease has been defined as a significant change in past research.[29] The impact of E-health on MED, as a continuous measure, will be evaluated in secondary analyses.

6.5.2 Secondary Outcome Measures

The secondary outcome measures are primarily self-report. Mobility can be an issue for individuals with chronic pain – to minimize participant burden, these data will be obtained through REDCap.[30] REDCap is a web-based software toolset and workflow methodology for collection and management of clinical research data.

1. Pain Intensity

The key secondary outcome is whether there is a clinically meaningful decrease (yes/no) in pain intensity (≥ 2 points) as measured by the Brief Pain Inventory (BPI)[31] at 6-month post-treatment follow-up. The BPI is a well-validated, reliable instrument that consists of a 4-item pain Intensity subscale and a 7-item pain interference subscale. The BPI has been used in more than 400 studies worldwide,[32] including the pilot trial (N=92) testing the efficacy of E-health for patients receiving opioid therapy.[25]

2. Pain-related Sleep Problems

The 3-item Sleep Problems Index will be used to assess sleep interference resulting from pain; this measure has been found to have good construct validity and reliability (Cronbach's $\alpha > 0.90$).[33]

3. Global Health

Global Health, which is a quality of life measure, will be assessed with the Patient-Reported Outcomes Measurement Information System (PROMIS) 10-item measure for Global Health, which briefly but comprehensively assesses physical, mental, and social health; this is a reliable (Cronbach's $\alpha > 0.80$) measure with demonstrated construct validity.[34]

4. Current Opioid Misuse

The Current Opioid Misuse Measure (COMM)[35, 36] will be used to assess opioid misuse. The COMM is a 17-item self-assessment used to monitor patients on opioid therapy and to assess whether patients are currently exhibiting behaviors indicative of misuse. The COMM has good predictive validity and reliability (Cronbach's $\alpha > 0.82$).[35, 36] Test-retest reliability has been established and construct validity demonstrated with positive correlations with urine toxicology results.[37]

5. Healthcare Utilization

The Stanford University Patient Education Research Center Health Care Utilization survey will be used to track health care utilization; the instrument has good test-retest reliability; validity has been established through chart audits.[38]

6.5.3 Moderators and Mediators

Our conceptual model of E-health's mechanisms of change is described in ***section 8.1***. The moderator and mediator measures are delineated below.

6.5.3.1 Neurocognitive Moderators

Obtaining the data for our hypothesized neurocognitive moderators (see ***Figure 2***) requires a web-based neurocognitive assessment. **WebNeuro**, which is the most widely used and validated web-based neurocognitive assessment,[39, 40] will be used for this purpose. WebNeuro, which takes 30 minutes to complete, assesses several functional domains including sensorimotor, attention, executive function, memory, and social cognition and also provides a measure of intelligence. WebNeuro reports raw scores and normative scores appropriately adjusted for the respondent's age, gender, and education. While WebNeuro includes a number of tests in addition to our moderators (Trail Making B and Delayed Verbal Recall), we selected it for use in this trial because it is the only web-based, validated neurocognitive assessment that included these desired tests. The additional WebNeuro tests may be used in exploratory analyses to generate hypotheses to be tested in future research. For example, impulsivity has been found to be predictive of opioid misuse as measured by the COMM in chronic pain patients.[41] We would attempt to replicate this finding by evaluating the relationship between the COMM and performance on WebNeuro's Go-no-go test, a measure of impulsivity.[40]

6.5.3.2 Mediators

Each of the following measures will be evaluated as mediators of E-health's treatment effect (see ***Fig. 2***).

1. Pain Knowledge Questionnaire

A prior RCT of E-health found that it significantly increased knowledge about chronic pain and pain management.[26] The Pain Knowledge Questionnaire includes questions about opioid medications and non-opioid treatment alternatives.

2. Pain Self-Efficacy Questionnaire (PSEQ)

The Pain Self-Efficacy Questionnaire (PSEQ) is a 10-item measure that has good construct validity and reliability (Cronbach's $\alpha = 0.92$).[42] Higher self-efficacy is associated with positive outcomes for pain coping, increased pain thresholds and tolerance,[43] decreased fear of movement, emotional distress, depressive symptoms, and disability.[44, 45]

3. Coping Strategies Questionnaire (CSQ-R)

This 27-item Likert-scale questionnaire assesses the use of six pain-coping strategies: 1) catastrophizing; 2) coping self-statements; 3) ignoring sensation; 4) distancing; 5) distraction; and 6) praying. Participants rate their utilization of each strategy on a 7-point scale (0-"Never do that" to 6-"Always do that"). The CSQ-R has been

found to have adequate internal consistency and validity in several patient populations.[46-49] The moderator to be tested in the proposed study is the use of passive coping strategies, calculated by combining the catastrophizing and praying subscales.[50]

4. Depression, Anxiety, and Stress Scales (DASS-21).

This 21-item Likert-scale questionnaire has established validity and reliability and assesses three constructs: 1) depression; 2) anxiety; and 3) stress.[51-53] Participants provide past-week ratings using a 4-point scale (0-"Did not apply to me at all" to 3-"Applied to me very much or most of the time").

6.5.4 Safety Measures

1. Adverse Events (AEs)

An adverse event (AE) for this trial testing a low risk, internet-based, intervention is defined as > 30% symptom deterioration from baseline as indicated by any of the following:

- Pain Intensity Score as measured by the Brief Pain Inventory
- Pain Interference Score as measured by the Brief Pain Inventory
- The Depression score from the Depression, Anxiety, and Stress Scales (DASS-21), and higher than Normal/Mild range
- The Anxiety score from the DASS-21, and higher than Normal/Mild range
- The Stress score from the DASS-21, and higher than Normal/Mild range

Within REDCap, a report identifying participants with potential AEs (i.e., > 30% worsening on the measures listed above relative to baseline) will be generated on a weekly basis at minimum.

6.5.5 Other Measures

6.5.5.1 Participant Measures

1. Demographics

This assessment will include questions about the participant's race/ethnicity, sex, marital status, education, and employment status.

2. Pain-related Diagnoses

Pain-related clinical characteristics will be assessed through both the participant's EHR data (e.g., pain diagnoses, co-occurring diagnoses) and through self-report.

3. Pain-related Treatment

Information about the TAU that the participant receives (physician visits, referrals for other treatments, etc.) will be assessed with the participant's EHR and through self-report. The self-report assessment will include questions about LOT, referrals received for nonpharmacologic treatment, and types of pain treatment utilized.

4. E-health program adherence

E-health program completion will be measured as a continuous variable by the presence of "star ratings," which are required when participants exit a learning activity in the E-health program. Consistent with scoring used in

a pilot study evaluating the E-health program,[25] an engagement level of "0" will be assigned if the pre-requisite activity in the initial "Understanding Pain" Learning Center was not completed; a "1" will be assigned if only the pre-requisite activity in the "Understanding Pain" module was completed; a "2" will be assigned if the Profile of Chronic Pain assessment is also completed, but there was no evidence of activity within any of the 4 other Learning Centers; a "3" will be assigned if activities were completed in 1 of the 4 other Learning Centers and so on, up to the highest level of "6" assigned if the participant has completed activities in all 4 other Learning Centers.

6.5.5.2 Clinical Practice Measures

TAU at the participating practices will be characterized using three assessments, which will be completed by an administrative person from each clinical practice. An attempt will be made to have the same person complete the assessments at the pre-recruitment and post-data collection assessment time points; individuals will be compensated between $50 and $100 for completing these assessments at each time point.

1. Clinical Practice Characteristics

A questionnaire will be used to obtain information about the general characteristics of each practice, including size (e.g., number of full-time equivalent providers, staff, patients), geographic location, and provider types (e.g., family medicine, internal medicine, nurse practitioners, etc.).

2. Practice-level Payer Data

A questionnaire will be used to obtain information about the payer types for each practice.

3. Assessment of Chronic Illness Care (ACIC)

A modified version of the Assessment of Chronic Illness Care (ACIC, version 3.5),[54] will be used to assess the practice's approach to treating chronic pain. The ACIC assesses six elements that encourage high-quality care as outlined in the Chronic Care Model.[55] The ACIC version 3.5 assesses: 1) health care organization (i.e., the degree to which the system focuses on chronic illness care); 2) community linkages (i.e., the degree to which linkages between the system and community resources have been established); 3) self-management support (i.e., the degree to which self-management by the patient is encouraged and supported); 4) decision support (i.e., the degree to which providers have access to evidence-based information); 5) delivery system design (this includes multiple aspects of the system including patient follow-up, encouraging a team-based approach etc.); and 6) clinical information systems (the degree to which providers and staff have timely information about individual patients and patient populations). In addition, the degree to which there is integration of these elements is assessed. The ACIC has been utilized in a number of quality improvement projects and has been shown to have adequate reliability and validity.[56, 57]

6.6 Randomization Plan

Eligible participants will be randomized in a 1:1 ratio to TAU or to TAU plus E-health (E-health^{+}). Randomization will be at the level of participants and stratified by site. The number in each treatment group will never differ by more than a factor of b/2 where b is the block size, which will help ensure treatment balance. The randomization process will be performed within REDCap and the randomization sequence will be unknown to the research staff.

6.7 Study Treatments

6.7.1 Treatment as usual (TAU)

TAU will primarily consist of LOT. Opioid dose, physician visits, and referrals to non-pharmacological treatments (e.g., physical therapy, behavioral therapy, etc.) will be tracked through the EHR. Participant self-report will also be used to assess whether the patient received referrals for nonpharmacologic treatment and the type of nonpharmacologic treatment(s) received. In addition, TAU will be characterized using three assessments (i.e., the ACIC and questionnaires about the general characteristics and payer types of the practice -see ***section 6.5.5.2***), which will be completed by an administrative person from each clinical practice.

6.7.2 E-Health

The E-health intervention is described in section 8. Participants randomized to the E-Health^{+} condition will receive a free, 4-month subscription to the on-line Goalistics Chronic Pain Management Program. E-health^{+} participants will receive e-mails outlining what activities they should be completing within the Chronic Pain Management Program during the course of their 4-month subscription and follow-up communications in the event of non-adherence.

7.0 STUDY PROCEDURES

7.1 Study Overview

Table 1 provides an overview of the participant procedures and assessments.

Table 1. Participant Procedures and Assessments

Assessment/Procedure	Scrn/ Base	Active Tx	Post-Randomization Follow-ups	
			4-Month	10-Month
4-month subscription for E-health		x		
Screening Assessments				
Informed consent	x			
Demographics	x			
Pain-related Diagnoses	x			
Efficacy Assessments				
Morphine Equivalent Dose	Electronic Health Record			
Brief Pain Inventory	x		x	x
Sleep Problems Index	x		x	x
Health Care Utilization Survey	x		x	x
Current Opioid Misuse Measure	x		x	x
PROMIS 10-item Global Health	x		x	x
Moderator/Mediator Assessments				
WebNeuro	x			
Knowledge about pain/opioids	x		x	x
Pain Self-Efficacy Questionnaire	x		x	x
Coping Strategies Questionnaire	x		x	x
DASS-21	x		x	x
Safety Assessments				
Adverse Events			x	x
Other Assessments				
Pain-related treatment	x		x	x
E-health Program Adherence		x		

EOT=End of Treatment; DASS=Depression, Anxiety, Stress Scale

7.2 Participant Recruitment and Consent

Potential participants will be identified through EHR queries. Our primary form of recruitment will be letters, which has been found to be an effective method of recruitment for trials testing online interventions in other conditions (e.g., obesity, etc.).[58] The recruitment letters will use an "opt-out" strategy in which patients are asked to contact the clinic if they do not wish to be contacted by research staff. An RCT comparing opt-out and opt-in (i.e., patient needs to

contact research staff if s/he is interested) strategies found the opt-out resulted in a significantly higher response rate and a more representative patient sample.[59] The opt-out strategy shows consideration for the patients' autonomy because it gives them ready access to more information about the study while also giving them the option to opt-out, whichever they decide.[60] Practice Facilitators (PFs) will ensure that identified potential participants are sent a recruitment letter and a study brochure. For patients not opting out, the PF will contact patients to inform them about the study and offer to complete a phone pre-screen. Patients who do not opt out, but who are not reached by phone may be sent an additional recruitment letter. If the patient passes phone pre-screen, they are sent an email directing them to a secure website for informed consent. Patients will be given the opportunity to discuss any questions or concerns with study staff prior to electronically signing the consent form. Patients who are interested in participating will sign the electronic consent form (e.g., using a mouse or touch screen). The time and date of signature is automatically recorded by the website. When a participant has signed the electronic consent, a secure e-mail notification will be automatically sent to research staff. Research staff will review the signed consent before sending an email with a link to the study screening assessments. Participants will be mailed a hard copy of their signed consent. Non-PHI information from all pre-screening interviews is retained to help track recruitment efforts and reasons for ineligibility. For individuals who do not qualify for the study, the other data collected during the pre-screening interview will be destroyed.

7.3 Screening/Baseline

After signing the informed consent form, the study participant will be sent an e-mail directing them to a website to complete the screening/baseline assessments. Participants who are potentially eligible based on the screening/baseline assessments will be sent an e-mail with a link for the web-based neurocognitive assessment (WebNeuro). Participants who meet study eligibility and complete screening/baseline (including WebNeuro) will be randomly assigned to the TAU or E-health^{+} condition. In some circumstances, the PI may allow individuals who do not complete WebNeuro to be randomized.

7.4 Active Treatment Phase

The active treatment phase is comprised of the 4 months during which E-health^{+} participants are provided with a free subscription to the Chronic Pain Management Program.

7.5 Follow-up

Because the primary outcome in this trial (MED calculated from opioid prescriptions) is contained in the site's EHR, it is not dependent on participant retention in the study. Thus, primary outcome data will be complete unless the participant withdraws consent or is no longer being treated at the clinical site. The secondary outcomes for this trial (i.e., online surveys at months 4 and 10), however, will primarily be patient-reported outcomes. The present trial will utilize multiple strategies to help ensure a high rate of completion. A recent systematic review of methods for retaining participants for follow-up in healthcare research found that studies using multiple retention strategies had significantly higher retention rates.[61] Accordingly, our retention plan includes several strategies identified by systematic reviews and meta-analyses to be associated with questionnaire completion in general research,[62] healthcare research and randomized controlled trials,[62-64] and trials of online interventions.[63] The retention strategies we will use include: 1) financial incentives conditional on survey completion;[63, 65] 2) minimal participant burden (i.e., online short-form assessments that can be completed at the participant's convenience over a 28-day period);[62, 64] 3) an established schedule of data collection windows provided to participants at the time of randomization;[62] and 4) a retention "escalation plan", which includes automated email reminders with links to complete surveys.[62, 64] Each of the follow-up time-points (4- and 10-months post-randomization) will have a 28-day data collection window during which the assessments can be completed. When the window begins, the participant will receive the initial assessment

invitation link via email. If the participant does not respond to the initial invitation, then the participant will receive up to 5 additional reminders, using a mix of emails, phone calls, and text messages, throughout the data collection window until it is completed. If a participant fails to respond to the 4-month follow-up survey within the allotted 28 days, then the participant will be sent a personalized retention letter via Certified Mail, approximately one week prior to the opening of the 10-month time-point's data collection window.

7.6 Trial Discontinuation

The study sponsor has the right to discontinue the investigation at any time.

7.7 Participant Reimbursement

Participants will also be reimbursed up to $110 for their time. Payments will be provided via a prepaid debit card.

Table 2: Reimbursement schedule

Study Measures	Estimated Time to Complete	Payment
Screening/Baseline	40 minutes	$30
WebNeuro	30 minutes	$20
4-months after randomization	40 minutes	$30
10-months after randomization	40 minutes	$30
Total	150 minutes	**$110**

8.0 CHRONIC PAIN MANAGEMENT PROGRAM (CPMP)

8.1 Program Development and Description

The Goalistics Chronic Pain Management Program, referred to as the E-health program in EMPOWER, was developed from cognitive, behavioral, interpersonal, and self-management interventions with demonstrated efficacy in traditional face-to-face or group settings. It is patient-centered, having been developed based on substantial input from people with chronic pain and chronic pain professionals. Specifically, in the initial project funded by the National Institute of Neurological Disorders and Stroke (NINDS), a prototype for the pain program was developed, reviewed, and twice revised. The second NINDS-funded project included the final development of the program and an RCT to test its efficacy.[26] The E-health program includes five learning centers - the order in which they are completed is customized for each user based on priorities identified from completing the Profile of Chronic Pain.[66] **Table 3** provides an overview of the content and therapeutic approach for each learning center. Developing new skills and integrating them into a patient's life requires practice and persistence on the part of the patient and the E-health intervention was designed to promote both. A set of self-management tools are integrated into the learning centers to enhance tracking, troubleshooting, and attainment of program activities and goals; examples of these E-health tools are provided in ***Table 4***. More in-depth information about the E-health program, including screen shots, can be found in ***Appendix A***.

Table 3. E-health learning center content and therapeutic approach
1. Thinking Better-Derived from cognitive models of pain management, this learning center teaches the person with chronic pain how to recognize, interrupt, challenge, and replace dysfunctional thinking. Users create a custom plan to decrease self-defeating thoughts while increasing effective thinking.
2. Feeling Better- Provides training in fundamental methods of emotion regulation, including identifying negative and positive emotional triggers, the role of relaxation training in emotion regulation, and incorporating positive emotional triggers into daily life. A set of relaxation sessions offer practice in using breathing as a trigger for relaxation, progressive muscle relaxation, guided imagery, and mindfulness meditation.
3. Doing More-The primary goals are to increase activity and exercise and promote goal-based activities. This learning center is based on behavioral and motivational models of pain self-management.
4. Relating Better- This is derived from interpersonal/transactional models of pain management. The user learns about types of social support and how to differentiate effective versus ineffective support. A personalized support plan is created.
5. Understanding Pain-This learning center teaches basic concepts underlying the biopsychosocial perspective on chronic pain and its management. It consists of a series of videos covering such topics as medication management, the safe use of pain medication, reducing reliance on pain medication, relaxation, cognitive behavior therapy, biomedical treatment options, and hypnosis.

Table 4. E-health tools to promote and track lifestyle changes
Navigator Calendar: Allows the user to schedule program activities and goals and send email and text-message reminders, with the ultimate goal that they will become automatic and self-sustaining.
Self-Monitoring Tool: Allows the user to select a self-monitoring exercise (e.g., monitoring positive emotions), schedule it on the calendar, and send automated email or text alerts throughout the day.
Pacing Tool: Used to create a custom plan to safely and slowly increase an activity over time. The user selects an activity to be paced (e.g., walking, swimming, meditating, etc.), identifies the amount of time it can be comfortably completed, and sets a target goal. The system creates a plan that increases the duration of the activity by 10% each week until the target time is reached.
Daily Check-In: Assists the user in tracking progress over time. This is also linked to a separate set of program features: **Mood Boosters, Pain Soothers**, and **Activity Boosters**. These tools allow the user to create a set of activities or experiences to boost mood, decrease pain, and increase activity. These are brief and easy-to-implement. Low mood, pain management, or activity ratings over several days triggers a reminder to schedule a Mood Booster, Pain Soother, or Activity Booster.
Self-Reward tool: Allows the patient to create a personalized list of inexpensive, easy-to-implement rewards to self-administer for progress and completing activities.
My Progress: Daily entries about what helps and interferes with activity completion are displayed, and compared to those of other program users to help the user understand his/her progress and to troubleshoot lack of progress. The system also displays progress in terms of Activity Completion Rate (the percentage of times that the user completed a scheduled activity). Each week, if the overall completion rate is reasonably high (e.g., ≥75%), a congratulatory message will be sent along with the suggestion that the user select a reward from his/her Self-Reward Menu.

8.2 Conceptual Model of E-health's Mechanisms of Change

Evaluation of potential moderators and mediators of E-health's effect on opioid medication use in chronic pain patients has been suboptimal due to the constraints of the small sample size of the pilot trial (N=92) and, in the first RCT (N=305), only data on prescription medication, rather than on opioid medication specifically, being collected. Thus, in addition to testing E-health's effectiveness, the proposed trial will make an important contribution by allowing us to test a model of E-health's mechanisms of change (see **Fig. 2)**.

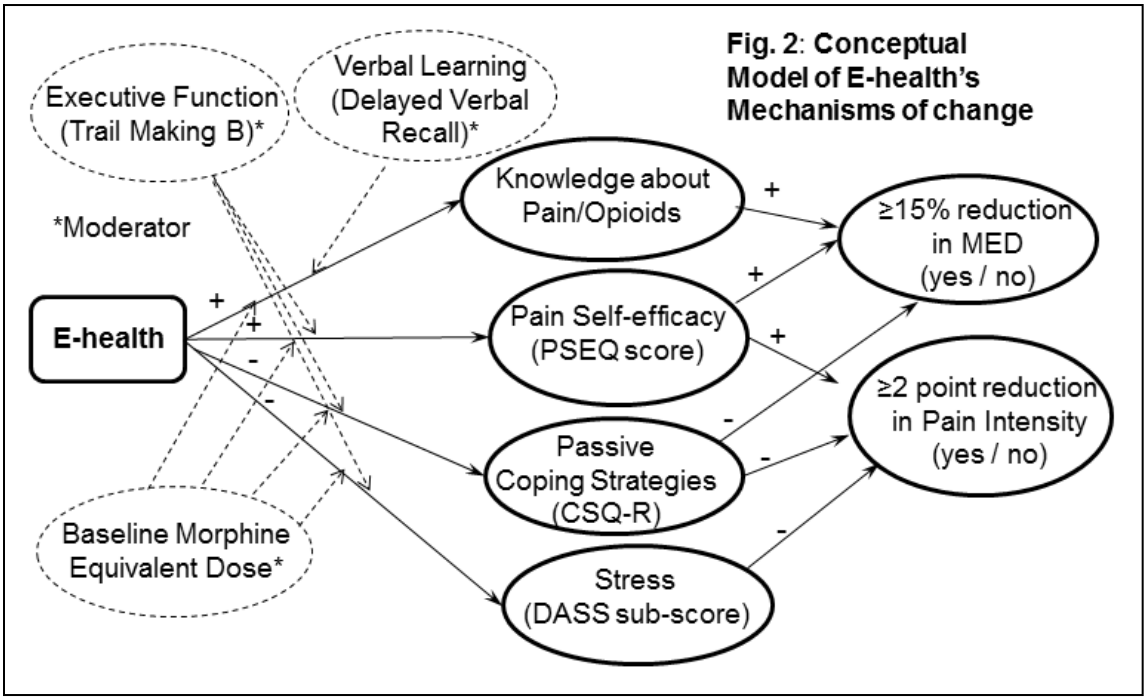


Fig. 2: **Conceptual Model of E-health's Mechanisms of change**

8.2.1 Hypothesized mediators

1) <u>Knowledge about chronic pain/opioid treatment</u> is significantly increased by E-health.[26] Knowledge about chronic pain/opioids has not, to our knowledge, been evaluated as a mediator of MED reduction; however, based on patient feedback, the information provided by E-health, particularly about the risks associated with opioids, decreases the perceived desirability of LOT.

2) Pain self-efficacy, as measured by the Pain Self-Efficacy Questionnaire (PSEQ), is significantly increased by E-health,[25] and associated with positive outcomes including pain coping,[44] increased pain thresholds and tolerance,[43] and decreased fear of movement and disability.[44, 45] In addition, in the pilot trial of E-health, PSEQ scores following treatment were positively associated with reduction in opioid medication use (r=.46, p=.03).[67]

3) Passive coping strategies. E-health significantly decreases pain catastrophizing, which is a passive coping strategy.[26] A role for passive coping strategies in pain outcomes is suggested by a recent trial evaluating the use of these strategies in the onset of chronic pain.[50] In that study, passive coping strategies prior to surgery, as measured by the pain catastrophizing and praying subscales of the Coping Strategies Questionnaire, predicted chronic pain intensity 12-months post-surgery.[50]

4) Stress. E-health significantly decreases stress, depression, and anxiety as measured by the Depression, Anxiety and Stress Scales (DASS) measure.[26] A recent study testing an on-line chronic pain program in patients with back, neuropathic, and/or arthritis chronic pain found that the stress scale of the DASS mediated the effects of the intervention.[52]

8.2.2 Hypothesized moderators

No consistent moderators of psychosocial pain-management interventions have been found despite multiple attempts to define such factors.[68] In their review of the literature, Day et al[68] noted that neurocognitive function may be an important moderator of psychosocial pain interventions but that it had yet to be evaluated. Similarly, Solberg et al.[69] hypothesized that a chronic pain patient's ability to self-regulate thoughts and emotions and to engage in active coping strategies relies, in part, on executive functioning; the authors further hypothesized that psychosocial interventions could fail in patients with insufficient executive functioning/self-regulation capacity.[69] Multiple studies have found cognitive impairment in chronic pain patients although the causal relationship between chronic pain and cognitive impairment is unclear. A recent meta-analysis of this literature revealed small-to-moderate effects in chronic pain patients for a subgroup of neurocognitive tests.[70] These tests include the Trail Making Test B (TMT-B; Cohen's d =-.38), a measure of executive functioning, and Delayed Verbal Recall (Cohen's d=-.57), a measure of verbal learning.[70] To better evaluate the potential relationship between cognitive function and pain, a recent study evaluated patients a month before a scheduled surgery and followed them up for a year post-surgery; TMT-B performance prior to surgery predicted the presence and intensity of chronic pain at 6- and 12-months post-surgery.[50] This finding is important in that it suggests that cognitive impairment may play a causal role in the development of chronic pain rather than being the result of pain or a side effect of medications used to treat pain. Consistent with Solberg et al.'s[69] hypothesized relationship between executive functioning and ability to self-regulate, this study also found that worse performance on the TMT-B was significantly associated with the use of passive coping strategies and that passive coping strategies predicted chronic pain intensity 12-months post-surgery.[50] Based on this literature, we hypothesize that participants with poorer executive functioning, as measured by the TMT-B, will have less capacity to learn self-regulation strategies from E-health (i.e., will moderate E-health's effects), and hence, will evidence less improvement in pain self-efficacy, stress and coping strategies. Our findings will be useful for determining how treatment options may need to be customized for individual abilities.

Another aspect of cognitive function that may moderate E-health's treatment effect is the ability to learn new information. Verbal learning ability, as quantified by Delayed Verbal Recall, measures the respondent's capacity to acquire, store, and retrieve verbal information.[71, 72] Better Delayed Verbal Recall performance is associated with greater health literacy and medication adherence.[73-75] Verbal learning test performance has also been found to be predictive of post-injury community integration,[76] job performance and employment status,[77, 78] and ability to benefit from a cognitive/social group intervention for Alzheimer's patients.[79] While ability to learn could impact the effect of E-health on all 4 hypothesized mediators, the strongest/clearest signal will

likely be for obtaining knowledge about chronic pain/opioid treatment; to reduce the risk of a Type-I error we will test verbal learning as a moderator only for knowledge acquisition.

Finally, there is a dearth of research evaluating the potential of MED as a moderator of treatment effect for chronic pain interventions. The participants in the present study will likely be on a wide range of MED at baseline (e.g., eligibility criteria require a minimum of ≥ 20 mg/day and do not set an upper limit). Baseline MED as a potential moderator of E-health's effects will be evaluated.

9.0 ANALYTICAL PLAN

9.1 Statistical Hypotheses

9.1.1 Primary Hypothesis

The primary hypothesis is that a significantly greater proportion of E-health^{+}, relative to TAU, participants will have a ≥15% decrease in MED between baseline and 10-month (i.e., 6-month post-treatment) follow-up.

9.1.2 Key Secondary Hypothesis

The key secondary hypothesis is that a significantly greater proportion of E-health^{+}, relative to TAU, participants will have a clinically significant decrease (i.e. ≥ 2 points[80]) in Pain Intensity score at 6 month post-treatment follow-up.

9.2 Intent-to-Treat Participant Population

The intent-to-treat population is defined as the participants who are randomized to treatment.

9.3 Analysis Plan

Each primary and secondary efficacy outcome measure will be analyzed for the intent-to-treat (ITT) population. While there is every intention to be complete in describing the analyses to be performed, it is not possible to anticipate every contingency, and some adjustments may be required to meet constraints posed by the structure of the data. Constraints such as non-linearity, non-normality, etc. may lead to different but more appropriate approaches to analysis. No interim efficacy analyses or adaptive features are planned.

All statistical tests will be conducted at the 5% Type I error rate (two-sided). When multiple tests are conducted, the chance of finding a significant difference in one of the tests, when in fact no difference exists, is greater than the stated Type I error rate. The investigators are aware of the multiple testing issues and will interpret results with caution and use confidence intervals where possible.

9.3.1 Primary Outcome

The primary hypothesis is that a significantly greater proportion of E-health^{+}, relative to TAU, participants will have a ≥15% decrease in MED between baseline and 10-month (i.e., 6-month post-treatment) follow-up. The MED outcome may be prone to site effects in that the strategies used by the healthcare system to treat chronic pain may influence prescribing behavior; thus, the primary analysis will test for potential site (UC Health vs. Duke) effects. Specifically, a logistic regression will test for treatment (E-health^{+} vs. TAU), site, and treatment-by-site interaction effects, with treatment being the effect of interest.

9.3.2 Secondary Outcomes

The key secondary hypothesis, that a significantly greater proportion of E-health^{+}, relative to TAU, participants will have a clinically significant decrease (i.e. ≥ 2 points[80]) in Pain Intensity score at 6 month post-treatment follow-up will be tested using logistic regression with treatment (E-health^{+} vs. TAU) as the effect of interest. For consistency with the primary analysis, models including site effects will be evaluated.

Most of the secondary outcomes consist of baseline-endpoint longitudinal variables, which can reasonably be treated as continuous numeric values. These will be analyzed using random-intercept mixed model regressions including treatment, time, and treatment-by-time interaction as predictor variables. For consistency with the primary analysis, models including effects of site will be evaluated. The impact of utilizing non-study chronic pain treatments (i.e., as self-reported on the pain-related treatment assessment or EHR), other than LOT, on decrease in MED and pain intensity (yes/no) will be tested with logistic regressions including treatment (E-health^{+} vs. TAU), use of other chronic pain treatment (yes/no), and their interaction. In the E-health^{+} group, the relationship between treatment adherence and outcome (e.g., MED, pain) will be evaluated with logistic regression with treatment adherence rating as the covariate.

9.3.3 Moderated Mediation Analyses

The purpose of the moderated mediation analysis is to explore the degree to which the model in ***Fig. 2*** is consistent with the obtained study results. Using all ITT data, we will perform mediation analysis[81] (empirically estimating 95% confidence intervals via bootstrapping) to test two mediation relationships: 1) knowledge about pain/opioids, pain self-efficacy, and passive coping strategies as joint mediators of the effect of E-health^{+} on MED reduction, and 2) pain self-efficacy, passive coping strategies, and stress as joint mediators of the effect of E-health^{+} on pain intensity score. We will test three potential moderators of E-health's treatment effect using linear regressions. One set of analyses will test whether executive function (as assessed by the Trail Making B) moderates E-health's effects on pain self-efficacy, passive coping strategies, and stress. The second will test whether verbal learning ability (as measured by the Delayed Verbal Recall test) moderates E-health's effects on knowledge about pain/opioids. The third will test whether baseline MED moderates E-health's effects on knowledge about pain/opioids, pain self-efficacy, passive coping strategies, and stress.

9.3.4 Safety Analyses

It is anticipated that AEs and SAEs will have a low frequency of occurrence in this low-risk trial. AE/SAEs will be presented in tabular form as a function of treatment arm

9.3.5 Missing Data

For any participant dropping out, an attempt will be made to ascertain the reason for dropout. Since the primary outcome is based on the EHR, it will be complete unless the participant withdraws consent or is no longer being treated at the clinical site. However, many of our secondary outcomes are at greater risk for missing values. REDCap Survey will use hard stops as needed to ensure that key patient-reported outcomes are completed. Data that remain missing despite these measures will be accommodated in our analyses and their impact gauged through sensitivity analysis. The models we will employ can be estimated without bias under the missing at random (MAR) assumption. We will assess whether missingness depends on observed measures by creating indicators of whether each variable was missing at each occasion where it should have been recorded, use logistic regression to find predictors of missingness, and report on differences in groups with complete vs. truncated follow-up. For analyses involving missing data, we will use multiple imputation to generate multiple complete datasets. The analyses specified above will be performed on each of these data sets, and the results will then be combined using standard rules to produce single inferences that reflect uncertainty due to missingness.

9.4 Sample Size and Power

The sample size calculation assumed an α level of 0.05 (two-tail). Study completion rates in the two prior E-health RCTs were 92.4%[26] and 79%.[25] Data completeness for our primary outcome measure, which is obtained from the EHR, is expected to be higher than the completeness of participant-completed assessments. The pilot RCT, which required participants to have an opioid prescription in order to be eligible, found that 21% of E-health, compared to 7% of wait-list control, participants reported decreasing or discontinuing their opioid medication;[25] this difference equates to an odds ratio (OR) of 3.6. While the proposed trial uses a different MED reduction outcome (≥15%) than the pilot (any reduction), the data from the pilot is the most pertinent available for estimating power. The EMPOWER trial has a target sample size of 400 (200/arm) participants – using a conservative estimated completion rate of 75% yields 300 total completers (150/arm). Having 300 completers would provide 80% power to detect an E-health^{+} treatment effect if ≥18% participants have a meaningful MED reduction (i.e., of at least 15%) against 7% of TAU participants having a meaningful MED reduction; this equates to an OR of ≥2.77.

9.5 Descriptive Statistics

Using graphical and numerical techniques, we will inspect the data to identify potentially outlying or high-leverage points, assess tenability of parametric assumptions, and evaluate the extent and pattern of missing data. Assessment of outliers and high-influence points will be conducted as residual analysis for specific statistical models, but data that appear extreme in preliminary analyses (e.g., boxplots; Q-Q plots) will receive particular attention in subsequent modeling. In models with continuous covariates, we will use scatterplots with non-parametric smoothing to detect substantial non-linear associations. Descriptive checks and exploration will therefore be integrated through the entire modeling process.

10.0 REPORTING AND MONITORING

10.1 Informed consent

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. Each study site must have the study informed consent approved by their IRB(s). Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of screening/baseline. Every study participant should be given a copy of the signed consent form.

Prior to signing the informed consent form, participants will be offered the opportunity to discuss the consent with research staff who are knowledgeable about the study. In order to ensure that potential study participants understand the research study, a comprehension “quiz” (referred to as a comprehension tool) will be administered to potential participants.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect a participants’ participation in the trial. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

Health Insurance Portability and Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance.

Investigator Assurances

Each site must file (or have previously filed) a Federal Wide Assurance (FWA) with the DHHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee.

10.2 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol must comply with their Institution's policy regarding conflict of interest.

10.3 Clinical monitoring

Each site will be responsible for implementing management and oversight activities during the pre-initiation, recruitment, enrollment, follow up, and close-out phases. These activities will be conducted by local project management staff/QA staff located at each site and aim to provide management support to the research team in order to ensure adherence to the protocol, SOPs, and regulatory requirements. The Lead Team will provide on-going monitoring of study progress and will hold regular study management meetings to monitor any emergent problems or ongoing problematic trends, and may additionally hold individual meetings with site staff in order to assist in resolving any site-specific problems that impact the study.

10.4 Study documentation

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms.

10.5 Safety Monitoring

10.5.1 Data and Safety Monitoring Board (DSMB)

A DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The DSMB will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment). A Data and Safety Monitoring Plan for the trial has been approved by the study sponsor.

10.5.2 Protocol Violations Reporting and Management

A protocol departure is any departure from procedures and requirements outlined in the protocol. Protocol departures may occur on two levels, deviation versus violation. The difference between a protocol deviation and violation has to do with the seriousness of the event and the corrective action required. A protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Protocol violations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Each site is

responsible for tracking and reporting to their IRB as required. Protocol deviations will be noted by participating sites and reported to their IRBs as required.

10.5.3 Confidentiality

To maintain participant confidentiality, study records and data will be stored in compliance with the International Conference on Harmonization (ICH) guidelines. Participant records will be held confidential by the use of study codes in the study database, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. No identifying information will be disclosed in reports, publications or presentations. Information collected for this study will be kept in a locked secure location accessible only to research staff and authorized personnel directly involved with this study.

10.5.4 Adverse Events (AEs)

An adverse event (AE) for this trial testing a low risk, internet-based, intervention is defined as> 30% symptom deterioration from baseline as indicated by any of the following:

- Pain Intensity Score as measured by the Brief Pain Inventory
- Pain Interference Score as measured by the Brief Pain Inventory
- The Depression score from the Depression, Anxiety, and Stress Scales (DASS-21), and higher than Normal/Mild range
- The Anxiety score from the DASS-21, and higher than Normal/Mild range
- The Stress score from the DASS-21, and higher than Normal/Mild range

Within REDCap, a report identifying participants with potential AEs (i.e., > 30% worsening on the measures listed above relative to baseline) will be generated on a weekly basis at minimum. A Central Research Staff member will contact any participants experiencing an AE to obtain additional information; during the process of obtaining additional information, the research staff will assess for potential SAEs. We will use FDA criteria for SAEs (i.e., an adverse event that results in any of the following outcomes: death, life threatening event, initial or prolonged hospitalization, disability, congenital anomaly, intervention to prevent permanent impairment or damage, or other significant medical event). All AEs/SAEs occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators in accordance with reporting requirements. Dr. Winhusen, for psychological AEs, and Drs. White or Dolor (or designated study physician), for SAEs, will manage all AEs/SAEs and make referrals for appropriate care, as necessary. All SAEs will be reported to the IRB of the participating sites and to the NIDA project officer within 72 hours of their discovery. All subject information will be de-identified when reporting SAEs.

10.5.5 Risk/Benefit Assessment

<u>Risks:</u>

• Breach of confidentiality: As with any study, there is a potential risk of loss of confidentiality. To maintain participant confidentiality, study records and data will be stored in compliance with the International Conference on Harmonization (ICH) guidelines. Participant-reported data will be collected through REDCap, which is HIPAA-compliant and 21 CFR Part 11- ready for audit trails for tracking data manipulation and exports. Neurocognitive assessment data will be collected through WebNeuro, which uses a secure website, with assigned unique user IDs and passwords, and no personally identifiable information will be collected by WebNeuro. EHR data will be transmitted by secure means to research staff. Emails or text messages between

researchers and participants, used in retention efforts, will be deleted after information exchange. We will train all study-related personnel to follow HIPAA regulations for research to ensure confidentiality of all data and that the rights of the patients are protected. All data will reside on password-protected computers, with only the investigators and key members of the research team having access. A variety of other measures will be taken to protect confidentiality, including: We will 1) assign a unique ID number to each patient to label all components of the protocol, instead of patient names, 2) restrict access to the key linking names and ID numbers to key staff and the PI at each site, 3) store any paper with data in a locked file cabinet. Participants will be told that agents of the IRB, QA monitors, and members of the DSMB will be allowed to inspect sections of their medical and research records related to this study, if requested.

• Emotional Discomfort: The participants may experience some emotional discomfort from answering sensitive and/or personal questions. There is the possibility that the participant will feel bored. The patient's ability to respond to study assessments in the privacy of his/her own home should help in reducing potential emotional discomfort. E-health is self-paced so patients can take breaks should any feelings of boredom arise.

• E-health risks: There is little to no risk associated with the E-health program, which has been found to be safe and efficacious in prior studies. However, we will be monitoring for adverse events as noted above.

Benefits: Previous research suggests that participants randomized to E-health^{+} may experience significantly greater decreases in pain severity, pain-related interference, perceived disability, depression, and pain-induced fear as well as significantly greater decreases in opioid misuse and MED. Other potential benefits include the chance to contribute to a scientific investigation which may benefit other patients like themselves in the future. The study will benefit society as a whole by potentially providing a low cost, accessible, multidisciplinary pain program to people with chronic pain that decreases opioid medication use and pain and improves pain self-efficacy. The risk/benefit ratio is favorable and conduct of the research well justified.

11.0 DATA MANAGEMENT

Four data collection systems will be used in this project. The management and merging of these data will be overseen by our research team members who have many years of experience in coordinating data from multiple sources for large multisite trials.

1) The vast majority of data will be patient-reported outcomes which will be collected through REDCap. This secure, flexible, web-based application provides: a) an intuitive interface for data entry and real time validation (e.g., automated data type and range checks); b) HIPAA-compliant and 21 CFR Part 11- ready audit trails for tracking data manipulation and exports; c) record locking and electronic signature functions; d) control of view/edit rights; e) a tool for reporting, monitoring and querying patient records; and f) automated export to common statistical packages. All participant-reported outcomes will be obtained via REDCap. In addition, the Central Research Staff will randomize participants to the E-Health^{+} or TAU-only arm, using REDCap's randomization module.

2) The WebNeuro system will be used to assess neurocognitive functioning. WebNeuro's vendor, Brain Resource Ltd., has an established history of providing valid, secure, web-based neurocognitive assessments for academic researchers. WebNeuro can be used on any computer that has an internet connection, a keyboard, and a mouse. Each participant will be assigned a unique user ID and password and no personally identifiable information will be collected. Upon completion of the tasks, participant data are transmitted via a secure website to the Brain Resource Central Analysis Facility for rapid and standardized scoring. The WebNeuro data will be provided to the data managers by the Brain Resource Ltd. in a secure format, and participants will be identified in the dataset by their unique user ID.

3) The sites' EHR will be used to identify potentially eligible participants, and to provide study data for randomized participants. All EHR data will be transmitted in a secure manner.

4) Participants randomized to E-Health^{+} will receive an email with: a link to the E-health tutorial videos and their study-assigned E-health username. Participant E-Health progress will be monitored by study staff via a secure, study-specific portal. When the study is complete, the E-health adherence data will be provided to the data managers by the E-health vendor (Goalistics) in a secure format, and E-Health^{+} participants will be identified in the dataset by their study-assigned E-health username.

12.0 PUBLICATION/DATA SHARING

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study also follows the policy that requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

13.0 SIGNATURES

Statement of Compliance
This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain IRB written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment in order to participate in the study. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

Typed Name	Signature	Date
Theresa Winhusen Principal Investigator	_____	_____
_____ Sub-Investigator	_____	_____
_____ Sub-Investigator	_____	_____
_____ Sub-Investigator	_____	_____

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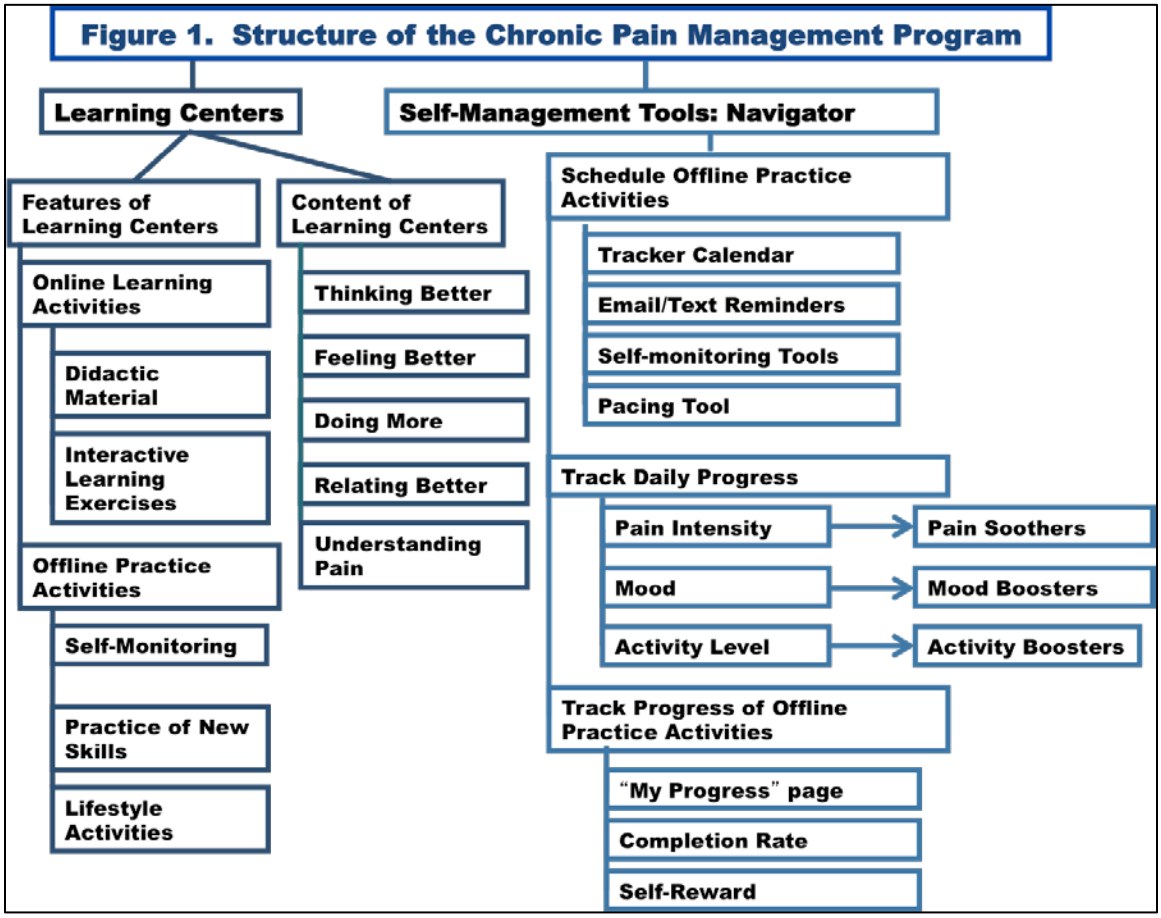
APPENDIX A: Goalistics Chronic Pain Management Program

1.0 Overview of the E-health intervention

Figure 1 depicts the two major components of the Goalistics Chronic Pain Management Program, referred to as the E-health program in EMPOWER. Program content is delivered via five Learning Centers. The Navigator contains the self-management tools, designed to help the user to move systematically through the program, set and track program goals, and monitor progress. This Appendix provides an overview of each of these program components.



1.1 Individually-tailored treatment plan

Program participants traditionally begin the program by completing the Profile of Chronic Pain, a comprehensive battery that evaluates pain status and history, coping strategies, pain attitudes and beliefs, interference with daily activities, and social responses to pain. The participant's scores are calculated and compared to national age- and gender-based norms. Based on this comparative analysis, a comprehensive report is provided and suggestions are made regarding the order of completion of the learning centers.

1.2 Help/guidance for using the E-health program

Program users vary in their computer abilities. A series of 13 Help Videos are available for the program user to assist with use of the program. In addition, participants may utilize a Feedback button or email us for technical support.

2.0 Learning Center Functionality

2.1 Features of Learning Centers

Learning Centers are comprised of online learning activities and offline practice activities. Each type of activity is briefly described below.

2.1.1 Online Learning Activities

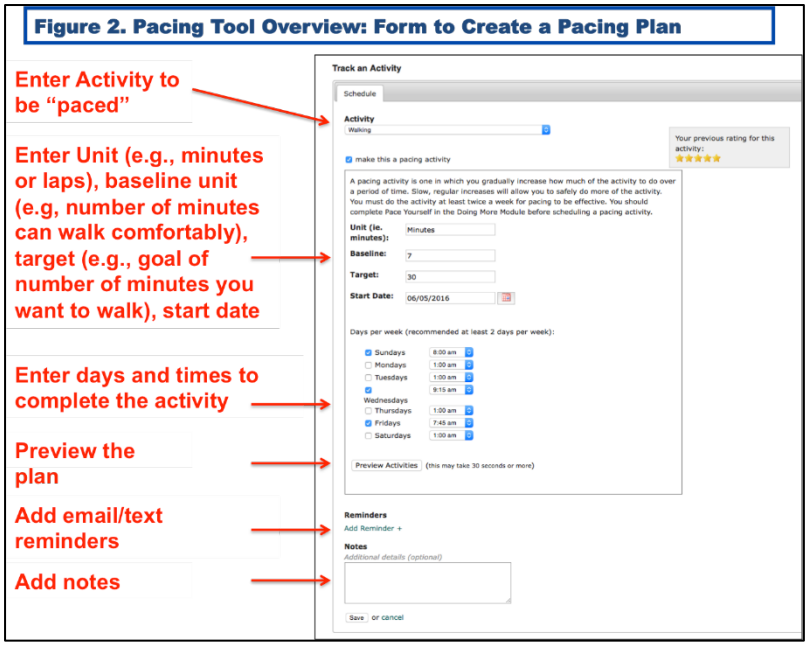
Each of the Interactive Learning Centers consists of a series of Online Learning Activities. Some are purely didactic and, in general, are presented as multimedia presentations to enhance interest and learning. Interactive learning activities may involve the presentation of basic concept(s) via text, pictures, diagrams, graphs, or video. The program user can interact with and practice the new material by answering questions or by creating personalized lists, journals, and/or plans. User data can be scored, graphed, tracked, reported, and sent to other parts of the program. Interactive activities are meant to increase the self-relevance of the program, hold the participant's attention, and to keep the user engaged with display of actual, real-time data in a way that is visual and easy-to-comprehend. An Online Activity often results in the scheduling of an Offline Practice Activity as described below.

2.1.2 Offline Practice Activities

Offline Practice Activities are scheduled and tracked via the Goalistics Navigator Calendar. There are three types of Offline Practice Activities:

1) Self-monitoring is an important component of behavior change, providing insight into problem areas at the outset, allowing for the prompt tracking of the nature and effectiveness of programmatic change, and for improving learning. A number of the learning centers employ self-monitoring as a means of gathering relevant, real-time information that the user will enter into the subsequent interactive activity. For example, in conjunction with the "Identify Positive Emotional Triggers" activity, the program user will use a program form to self-monitor positive emotions over a period of two days to identify experiences that trigger positive emotions. Each day, the user will receive 5 prescheduled reminders to implement the self-monitoring.

Figure 2. Pacing Tool Overview: Form to Create a Pacing Plan



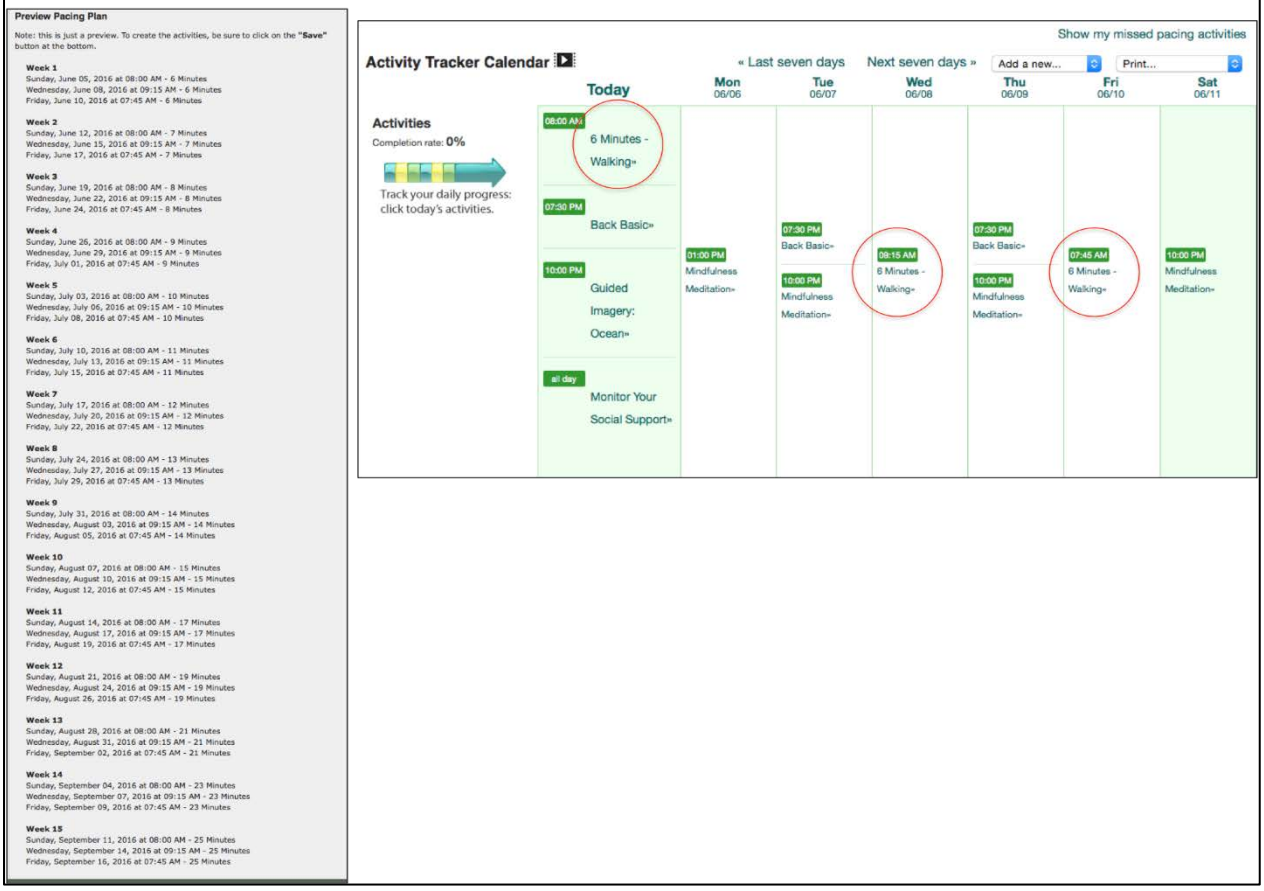
2) Practice of a new skill (e.g., social engagement) is an essential component of behavioral change programs.

3) Having learned and practiced the underlying skills of the CPMP, the user will transition to the incorporation of lifestyle activities (e.g., exercise) into his or her daily life. A number of program objectives involve lifestyle changes, such as increased exercise, regular relaxation sessions, or more active social engagement. By scheduling and tracking such activities via the Navigator Calendar (see below), the ultimate goal is that these activities will become automatic and self-sustaining.

Some of the offline activities utilize the Pacing Tool. The Pacing Tool is used to create a custom plan to safely and slowly increase an activity over time. The user selects an activity to be paced (e.g., walking, swimming, meditating, spending time socializing, time sitting at the computer), identifies the amount of time it can be comfortably completed (baseline), selects a target goal, and chooses weekly days/times to

complete the activity. The system then creates a plan that initially backs the patient off of baseline by 10%, then increases the duration of the activity by 10% each week until the target time is reached. Figure 2 shows screenshots of the Pacing Form; Figure 3 displays a sample Pacing Plan (showing weekly schedule and increases), and the paced activities that were automatically scheduled on the Calendar.

Figure 3. Pacing Tool Overview: Pacing Plan and Display of Paced Activity on Calendar



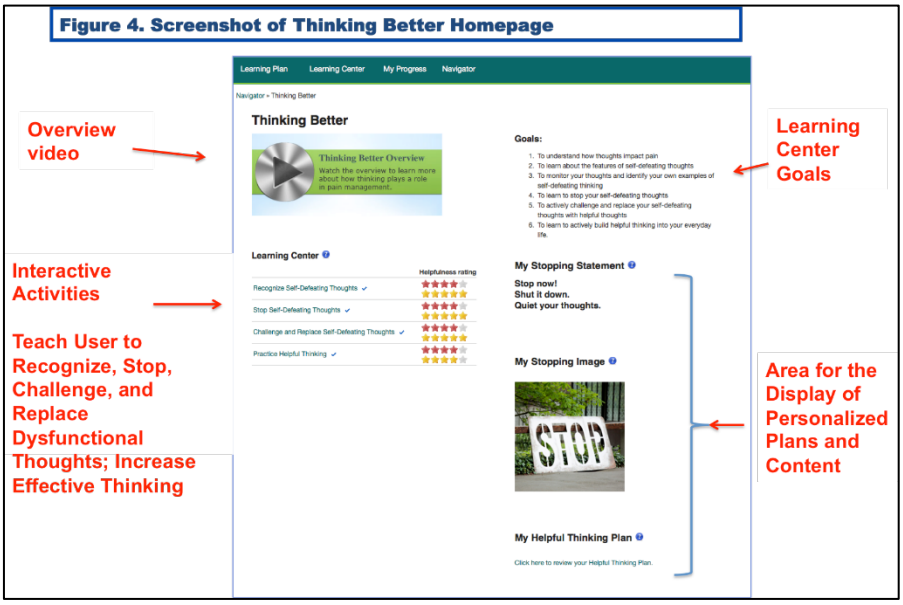
3.0 Learning Center Content

The five learning centers are described below. The content and interactive activities are derived from cognitive-behavioral, interpersonal, motivational, educational, and self-management models of chronic pain and strategies for therapeutic change. Note that we did not "invent" new interventions; rather we transformed evidence-based, face-to-face strategies into an online format.

3.1 Thinking Better

Derived from cognitive models of pain management, this learning center teaches the person with chronic pain how to recognize, interrupt, challenge, and replace dysfunctional thinking. Users create a custom plan to decrease self-defeating thoughts while increasing effective thinking. Figure 4 provides an annotated screenshot of the Thinking Better home page. Each of the learning centers is organized in the same way, as indicated in Figure 4. An overview video presents the underlying rationale and basic concepts to be learned in the center. The learning center goals and links to each of the interactive activities are included. A custom area on the bottom right of the page displays personalized content and links to custom plans.

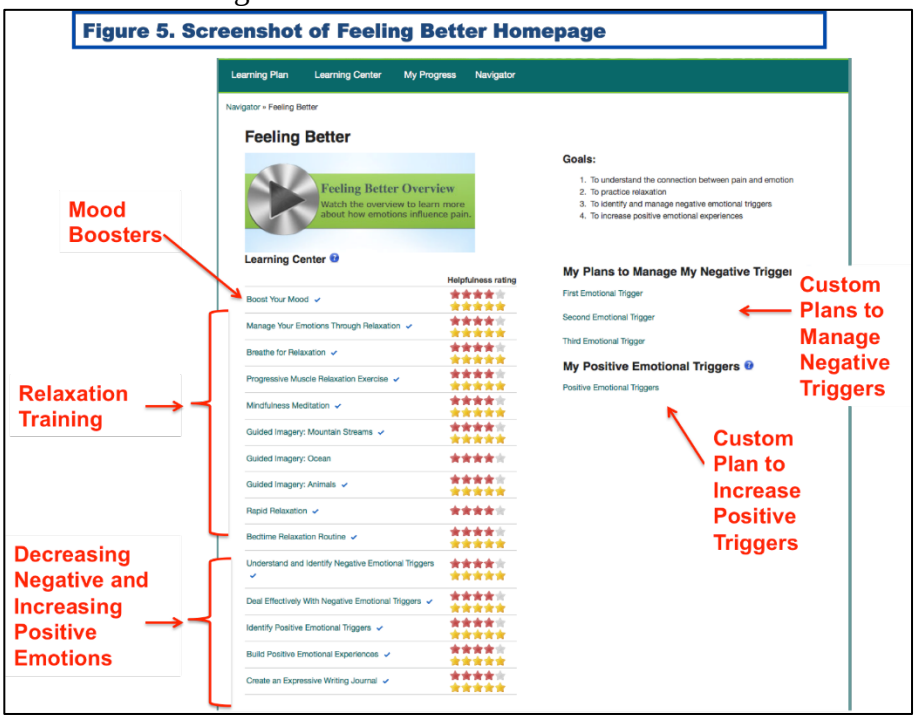
Figure 4. Screenshot of Thinking Better Homepage



3.2 Feeling Better

This learning center provides training in fundamental methods of emotion regulation, including identifying negative and positive emotional triggers, the role of relaxation training in emotion regulation, and incorporating positive emotional triggers into daily life. A set of relaxation sessions within the center, offer practice in using breathing as a trigger for relaxation, progressive muscle relaxation, guided imagery, and mindfulness meditation. See Figure 5 for an annotated screenshot.

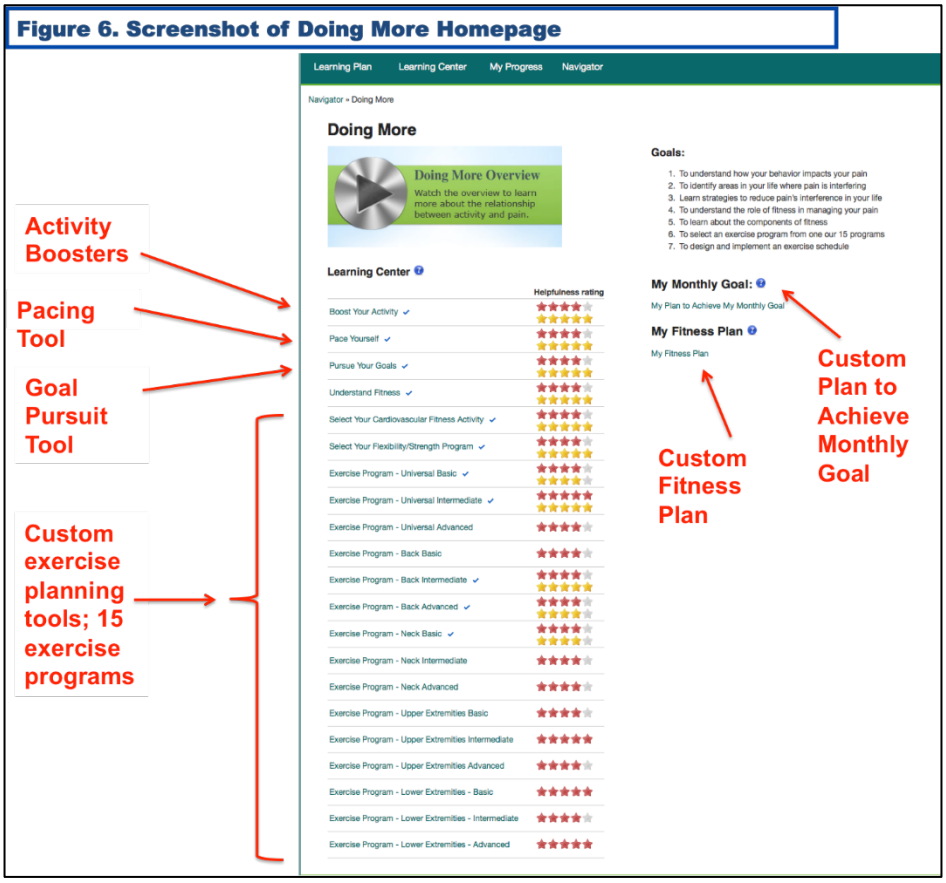
Figure 5. Screenshot of Feeling Better Homepage



3.3 Doing More

The primary goals of Doing More are to increase activity and exercise and promote goal-based activities. This learning center is based on behavioral and motivational models of pain self-management. As shown in the annotated screenshot (Figure 6), Doing More contains a tool to boost activity, a pacing tool, and a goal pursuit tool. The user creates a plan to pursue a personal goal each month and completes two activities that result in the creation of a personalized fitness plan involving both cardiovascular activity and one of our 15 flexibility/strength programs (created by a physical therapist and physical medicine/rehabilitation physician).

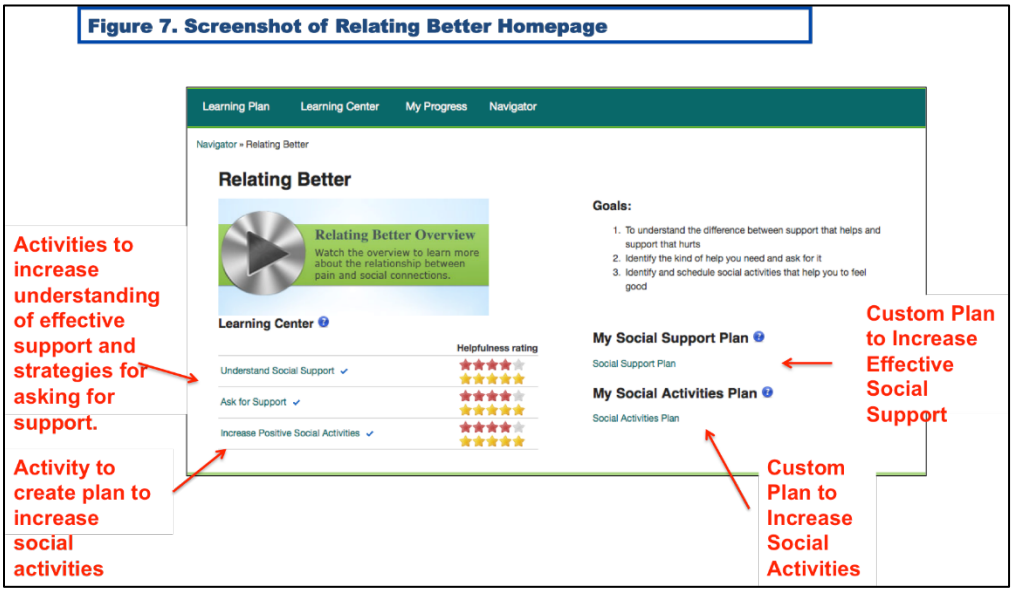
Figure 6. Screenshot of Doing More Homepage



3.4 Relating Better

This learning center is derived from interpersonal/transactional models of pain management. The program user learns about types of social support and how to differentiate effective versus ineffective support. A personalized support plan is created. The importance of engaging in positive social engagement is discussed and the user creates a plan to increase social activities. See the annotated screenshot in Figure 7.

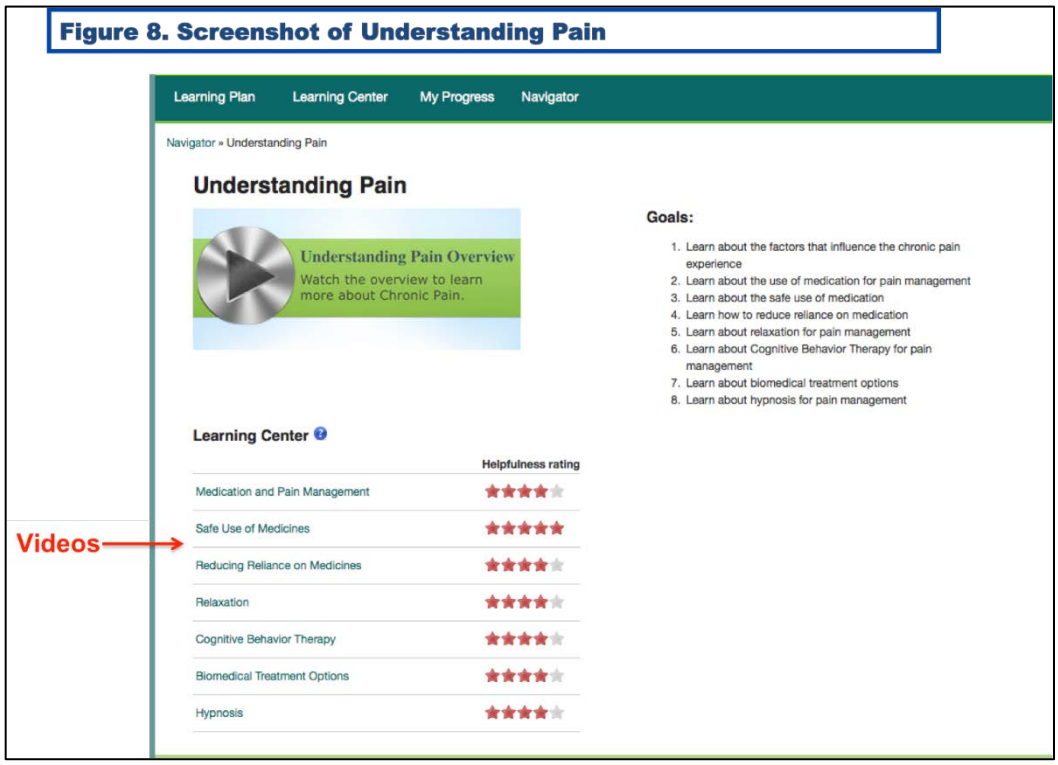
Figure 7. Screenshot of Relating Better Homepage



3.5 Understanding Pain

This learning center teaches basic concepts underlying the biopsychosocial perspective on chronic pain and its management. It consists of a series of videos covering such topics as medication management, the safe use of pain medication, reducing reliance on pain medication, relaxation, cognitive behavior therapy, biomedical treatment options, and hypnosis. See the annotated screenshot in Figure 8.

Figure 8. Screenshot of Understanding Pain



4.0 E-health Navigator

The foundation of the Chronic Pain Management Program is goal setting and self-management. The learning activities of the E-health intervention focus on a consistent goal-based process of learning new information, practicing it online and offline, tracking progress, troubleshooting problems, and incorporating newly learned material into daily life. The Navigator (see Figure 9 for screenshot) delivers the self-management tools of the E-health intervention including Activity Scheduling, Tracking of Daily Progress, and Tracking of Progress of Offline Practice Activities. A brief overview of each component follows.

4.1 Activity Scheduling

The Navigator Calendar allows the user to schedule program activities and goals, send email and text-message reminders, and use other basic calendar functions. The Self-Monitoring Tool is built into the calendar and allows the user to select a self-monitoring exercise (e.g., monitoring positive emotions), schedule it on the calendar, and send automated email or text alerts throughout the day.

4.2 Tracking of Progress via Daily Check-In

Daily Check-In is a key capability of the Navigator designed to assist the user in tracking progress over time. Using a visual 5-star rating scale, the program user rates mood, pain management, and activity level. As displayed in Figure 9, the three ratings are displayed in a color coded, 30-day graph, allowing the user to track progress and to observe relationships among the variables. As users complete the learning centers, they will be able to visually track improvements. Note that the Daily Check-In is linked to a separate set of program features: Mood Boosters, Pain Soothers, and Activity Boosters. These tools allow the user to create a set of activities or experiences to boost mood, decrease pain, and increase activity. For example, a Mood Booster is defined as indicated in Figure 10 and mood boosters are created as shown in Figure 11. They can then be added to the calendar as needed. Pain Soothers and Activity Boosters are also easy-to-implement, brief activities to provide a noticeable reduction in pain or increase in activity. Low mood, low pain management, or low activity ratings in the Daily Check-In over several days will trigger a reminder to schedule a Mood Booster, Pain Soother, or Activity Booster.

Figure 9. Screenshot of Navigator

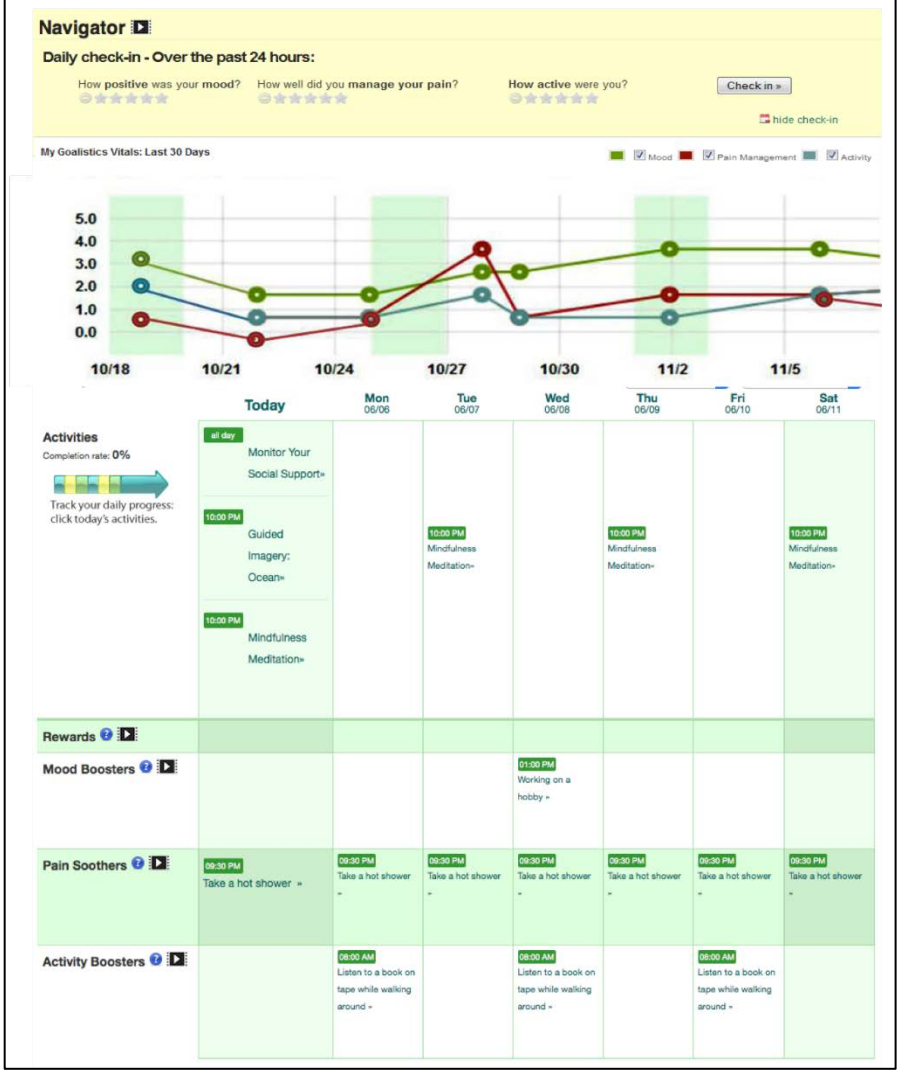


Figure 10. Definition of Mood Booster

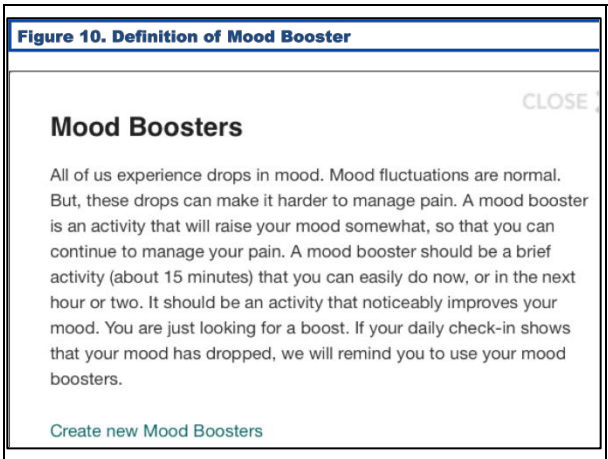
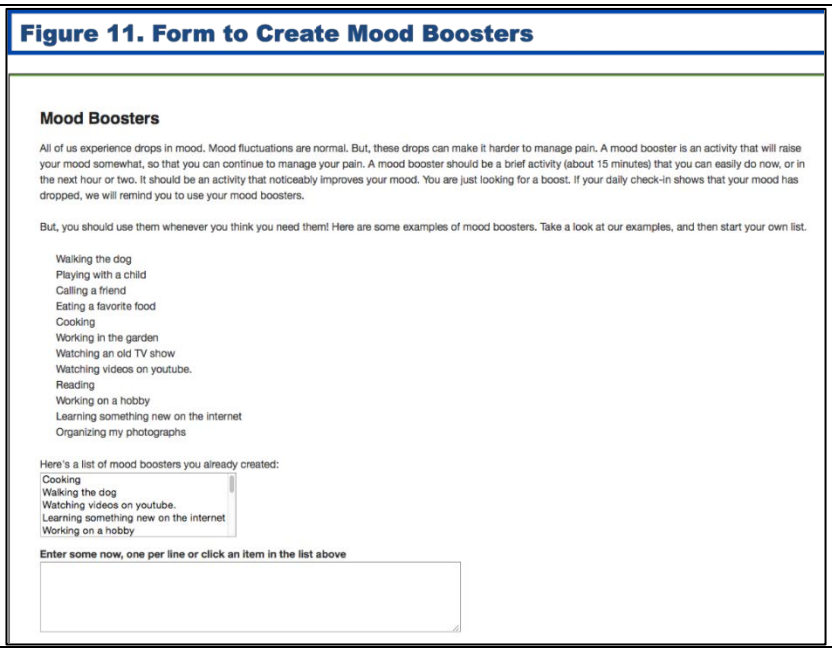


Figure 11. Form to Create Mood Boosters

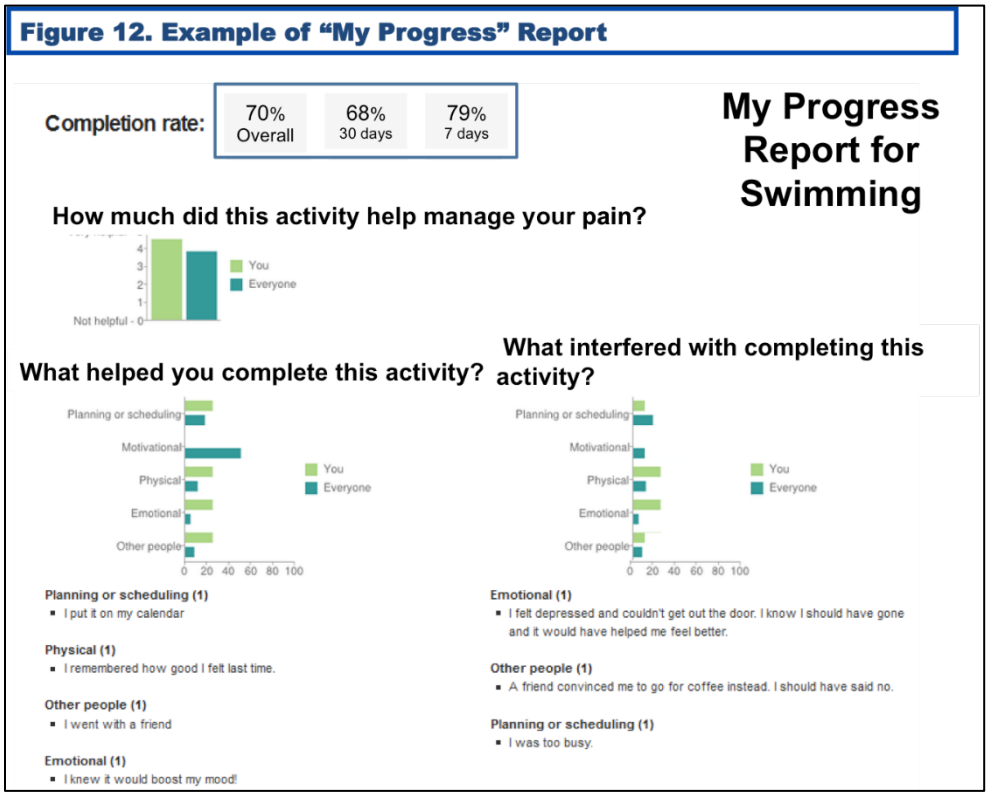


4.3 Track Progress of Offline Practice Activities

The user can monitor daily progress by recording whether scheduled program activities were completed or not completed. If the user completed the activity, s/he is asked to indicate how helpful it was and how much the activity helped the user move closer to the Learning Activity goal. In addition, the user will be asked what facilitated the completion of the activity. On the other hand, if the user is unable to complete a daily activity, he/she will be asked to indicate what specifically interfered with activity completion.

All of the above information is automatically compiled on an Activity Detail Page in the My Progress section of the Navigator, a critical source of information to help the user stay on track. Daily entries about what helps and interferes with activity completion are displayed, and compared to those of other program users. This information will help the user to understand his/her progress and to troubleshoot lack of progress. The system also displays progress in terms of Activity Completion Rate, the percentage of times that the user completed a scheduled activity. Each week, if the overall completion rate is reasonably high (e.g., 75% or greater), a congratulatory message will be sent along with the suggestion that the user select a reward from his/her Self-Reward Menu: a personalized list of rewards generated by the user. The tool is similar in structure to the Mood Boosters, Pain Soothers, and Activity Boosters tools. The Self-Reward tool allows the patient to create a personalized list of inexpensive, easy-to-implement rewards to self-administer for progress and success within the program. See Figure 12 for a sample My Progress report.

Figure 12. Example of "My Progress" Report



Supplement 2 Table. Results from multiple imputation analyses testing for treatment effects on self-report measures

	Test [A]	p [A]	OR/d (95% C. I.) [B]
BPI Pain Intensity (≥ 2 points)	2.2	**0.0278**	OR= 2.227 (1.091 - 4.543)
BPI Pain Interference (≥ 2 points)	1.86	0.0636	OR= 1.643 (0.972 - 2.776)
BPI Pain Intensity	-0.9	0.3702	d=-0.123 (-0.392 - 0.146)
BPI Pain Interference	-1.23	0.2197	d=-0.252 (-0.655 - 0.151)
PROMIS Global Physical Health	1.04	0.2964	d=0.556 (-0.488 - 1.599)
PROMIS Global Mental Health	0.07	0.9480	d=0.043 (-1.249 - 1.335)
Current Opioid Misuse Measure	0.02	0.9801	d=0.014 (-1.111 - 1.139)
Pain Knowledge (% Right)	3.32	**0.0009**	d=0.037 (0.015 - 0.059)
Pain Self-Efficacy	2.67	**0.0076**	d=2.875 (0.765 - 4.986)
Coping Strategies:			
Catastrophizing	-2.05	**0.0400**	d=-0.208 (-0.406 - -0.010)
Coping Self Statements	1.23	0.2181	d=0.121 (-0.072 - 0.314)
Distance from Pain	1.91	0.0566	d=0.253 (-0.007 - 0.514)
Distraction	3.17	**0.0015**	d=0.332 (0.127 - 0.538)
Ignoring Pain	1.24	0.2146	d=0.138 (-0.080 - 0.355)
Praying	-1.26	0.2073	d=-0.155 (-0.396 - 0.086)
Passive Coping [C]	-2.1	0.0359	d=-0.372 (-0.720 - -0.024)

[A] Linear Regression Type-I Wald t test for treatment effect for baseline-posttest difference (**Bold** text indicates $p < .05$.)

[B] Odds ratio or Cohen's d for baseline-posttest difference

[C] Passive coping includes catastrophizing and /or praying.

BPI Brief Pain Inventory; PROMIS Patient-Reported Outcomes Measurement Information System

Data Sharing Statement

Data available: Yes

Data types: Deidentified participant data

How to access data: winhust@ucmail.uc.edu

When available: With publication

Supporting Documents

Document types: None

Additional Information

Who can access the data: researchers whose proposed use of the data has been approved

Types of analyses: for a specified purpose (meta-analysis of study variables)

Mechanisms of data availability: after approval of a proposal, additional IRB approval (if necessary) and signing of a data access agreement