Treating Opioid Patients' Pain and Sadness (TOPPS)

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1 List of Abbreviations

Abbreviation	Abbreviation definition
TOPPS	Treating Opioid Patients' Pain and Sadness
HE	Health education
BHS	Behavioral Health Specialist
OBAT	Office-based addiction treatment
BHS	Behavioral Health Specialist
RA	Research Assistant
CAM	Complementary and Alternative Medicine
OUD	Opioid Use Disorder
BA	Behavioral Activation
ACT	Acceptance and Commitment Theory
BPI	Brief Pain Inventory
VAS	Visual Analog Scale
PHQ-9	Patient Health Questionnaire-9
BADS	Behavioral Activation for Depression Scale
PASS	Pain Anxiety Symptoms Scale
SOP	Standard Operating Procedure
MSSI	Modified Scale for Suicidal Ideation
SCID	Structured Clinical Interview for DSM
SSTAR	Stanley Street Treatment and Resources
BMC	Boston Medical Center
BU	Boston University
BUP	Buprenorphine
EHR	Electronic Health Records
CDW	Clinical Data Warehouse
MOUD	Medications for Opioid Use Disorder
RW	Risa Weisberg (PI)
AE	Adverse Event
SAE	Serious Adverse Event
DSMB	Data Safety and Monitoring Board
IRB	Institutional Review Board
CRF	Case Report Form
MICE	Multiple imputation by chained equation
MAR	Missing at random
SEM	Structural Equation Models
ICH	International Council for Harmonization

2 Protocol Summary

Title:	Treating Opioid Patients' Pain and Sadness (TOPPS)
Population:	163 participants currently being treated with buprenorphine

Intervention:	Intervention: 12-week lifestyle psychoeducation about pain, depression, and opioid use; as well as values-based, behavioral activation to increase engagement in meaningful activities. Timing: 3-months Method: Randomized controlled trial
Objectives:	1) to determine whether the TOPPS intervention, compared to HE, results in less pain interference and pain severity over the 3-month treatment phase; 2) to determine whether TOPPS, compared to HE, results in less depressive symptoms over 3 months; 3) to determine whether TOPPS, compared to HE, results in sustained improvements in pain interferences, pain severity, depressive symptoms, and buprenorphine treatment retention (self-reported continuous treatment) over the 12 months of the study.
Design/Methodology:	163 participants who are currently being treated with buprenorphine and who endorse pain and depressive symptoms were randomized into the trial. Recruitment occurred from two primary care, office-based addiction treatment (OBAT) buprenorphine clinics, as well as through online advertisement. Following consent and the baseline interview, participants were randomized to one of two study arms: the TOPPS intervention or health education. The TOPPS intervention consists of 3 main components: 1) psychoeducation about pain, depression, opioid use, their interactions, and the role of avoidance; 2) coaching in how to be an informed, activated patient; and 3) values-based, behavioral activation, to increase engagement in meaningful activities. The intervention is a total of 6 phone-based sessions over 12 weeks with a Behavioral Health Specialist (BHS). The control arm (health education) involves six sessions led by the same BHS. The first health education session is titled "What to Eat." Participants then select five additional topics, one for each of the remaining sessions. Topics include, "What Not to Eat," "Colds, Germs, and Flu," "Preventing Cancer," "Diabetes," "Protecting your heart," "Getting a Good Night's Sleep," "Complementary and Alternative Medicine (CAM)," "Caffeine," and "Physical Activity." Follow-up interviews are conducted by trained Research Assistants (RAs) at 1, 2-, 3-, 6-, 9-, and 12-months (for participants enrolled prior to XX) post-enrollment.
Total Study Duration:	5 years
Subject Participation Duration:	9-12 months

3 Background/Rationale & Purpose

3.1 Background Information

An estimated 1.7 million adults used prescribed buprenorphine in 2019 [1]. >40% of those individuals have pain that interferes with daily activities and affects buprenorphine treatment outcomes [2].

Approximately 29–48% of individuals with substance use disorder are estimated to have depression [3,4]. Further, depression and pain often co-occur, with estimates of up to 72% of people with chronic pain meeting criteria for depression [5]. Though both pain and depression are common among patients with OUD (Opioid Use Disorder), these conditions often go unaddressed [6]. There are limited non-pharmacological treatments available with the goal of improving pain outcomes. Furthermore, pain can interfere with effectiveness of antidepressants [7,8]. However, addressing pain or depression alone can be ineffective for patients suffering with both [9]. Studies have demonstrated that behavioral interventions are effective in patients with comorbid conditions, including substance use, depression, and chronic pain [10].

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and policies and procedures of the Boston Medical Center and Boston University Medical Campus Human Research Protection Program and of the Institutional Review Board of Boston University Medical Campus

3.2 Rationale and Purpose

We sought to develop and study an intervention to address this commonly occurring and often debilitating triad of conditions, pain, depression, and opioid use disorder. The TOPPS (Treating Opioid Use, Persistent Pain, and Sadness) intervention integrates and builds upon existing behavioral therapies for chronic pain and depression. Studies have shown that behavioral activation (BA) and values-based approaches such as Acceptance and Commitment Therapy (ACT) are efficacious treatments for chronic pain and depression [11,12]. Behavioral activation is frequently used in treatments for chronic pain and depression to counteract behavioral avoidance that interferes with daily functioning by increasing engagement with valued and enjoyable life activities [13]. BA therapy and ACT have demonstrated reductions in pain interference, stress, depression, and pain-related anxiety [14,15]. Similar to the ACT model, the TOPPS intervention supports participants in clarification of personal values, long and short-term goal setting and behavioral activation in service of these values, and nonjudgmental acceptance of experiences as they pursue their goals.

We have performed two promising pilot trials addressing pain depression together in vulnerable populations. The first involved persons living with HIV (N = 58) [16]. A more recent randomized trial (N =21) of TOPPS in persons receiving buprenorphine at two primary care sites showed promising decrements in pain interference with daily activities and pain severity when compared to the Health Education (HE) control condition. We thus planned to further evaluate the effectiveness of TOPPS in a fully powered trial. The TOPPS intervention includes psychoeducation about pain, depression, and opioid use; as well as values-based, behavioral activation to increase engagement in meaningful activities. The main study outcomes are reduced and sustained pain severity, pain interference, depressive systems, and buprenorphine treatment retention.

4 Objectives

4.1 Study Objectives

The described study is a randomized clinical trial of the Treating Opioid Use, Persistent Pain, and Sadness (TOPPS) intervention compared to health education (HE) contact-control condition among

persons receiving buprenorphine for opioid use disorder. The study objectives are as follows: 1) to determine whether the TOPPS intervention, compared to HE, results in less pain interference and pain severity over the 3-month treatment phase; 2) to determine whether TOPPS, compared to HE, results in less depressive symptoms over 3 months; 3) to determine whether TOPPS, compared to HE, results in sustained improvements in pain interferences, pain severity, depressive symptoms, and buprenorphine treatment retention (self-reported continuous treatment) over the 12 months of the study. Mechanisms by which TOPPS may reduce pain interference will also be examined, including 1) (increased) activities of engagement); 2) (decreased) avoidance of meaningful life activities; and 3) (decreased) fear of pain.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

The primary aim of this study is to test the hypothesis that participants randomized to the TOPPS intervention, compared to the Health Education condition will 1) have less pain interference and pain severity, as measured by the BPI (Brief Pain Inventory) and a Visual Analog Scale (VAS) at the end of the 3-month treatment phase.

4.2.2 Secondary Outcome Measures

- **Depression**

  The PHQ-9 (Patient Health Questionnaire-9) will be used to measure depression severity and suicidality. It is a commonly used clinical interview that yields a depression severity score between 0 and 27.

- **Buprenorphine treatment retention**

  Buprenorphine treatment retention will be measured via chart review and participant self-report.

4.2.3 Exploratory Outcome Measures

We will examine potential mediators of change in our primary outcomes during the 3- month treatment period, decreased avoidance of life activities (BADS [Behavioral Activation for Depression Scale]), and decreased pain anxiety or fear of pain (PASS [Pain Anxiety Symptoms Scale]).

5 Study Design

Eligible participants will be adult men and women currently receiving buprenorphine. Participants will be randomized to either *the TOPPS intervention* or a health education intervention (*HE*). We will provide both interventions over three months and follow participants for a total of 9 months in order to observe both short-term and longer-term effects of *the intervention*. Participants are recruited from two primary care, office-based addiction treatment (OBAT) buprenorphine clinics in New England: a large, university-affiliated, hospital-based clinic and a community health center's buprenorphine program. In October 2021, during the COVID-19 pandemic, recruitment was expanded to include targeted online advertisement primarily seen on social media sites, facilitated by BuildClinical LLC, a private software platform. After confirming study eligibility, the RA administers and documents informed consent within 14 days of the participant screening eligible. Prior to March of 2020, informed consent procedures

occurred in-person and took place on the same day as the participant's baseline visit. All onsite research activities were paused at the onset of COVID-19 pandemic. Remote research activities resumed in October of 2020. At that time, the study team transitioned all research activities to be conducted over the phone and via mail. Informed consent is collected via an e-consent form. Upon signing of the informed consent, a subsequent baseline interview is scheduled. Eligible participants are administered the assessment and are randomized to one of the two study arms upon completion of the interview. Randomization is stratified on three factors: study enrollment site, disability status, and currently taking an antidepressant medication using randomly permuted blocks. There is a 1:1 random allocation of the intervention between the study groups. Follow up interviews are conducted by trained RAs at 1-, 2-, 3-, 4-, 6-, 9-, and 12-months (for participants enrolled prior to October 2023) post-enrollment.

6 Potential Risks and Benefits

6.1 Risks

There are four major areas of risk:

- **Confidentiality and loss of privacy**. Study personnel will be collecting considerable information about the study participants. This may create some distress and could cause social and psychological risk if released inappropriately. This risk is a serious one but we believe that it is highly unlikely. We have extensive experience taking measures appropriate to safeguarding confidential information.
- **Increased distress due to assessment or intervention procedures.** It is possible that some patients will experience increased intrapersonal or interpersonal psychological distress as a result of participating in assessment or intervention. Psychological risks of TOPPS may include discomfort with attention to unpleasant thoughts, feelings or body sensations. Some individual may experience an initial increase in undesirable feelings with increased attention to them. However, participants are self-guided and are encouraged to set their own limitations. In addition, the intervention is specifically geared towards dealing with such discomfort. In the vast majority of cases, we believe that any increased distress experienced will be mild and transitory in nature.
- **Ineffective intervention**. It is possible that some participants will not experience improvements in pain or depression-related outcomes OR will experience clinical deterioration or suicidality
- **Potential coercion**. It is possible that individuals may feel coerced into participating. This risk is a serious one but we believe that it is highly unlikely given informed consent processes and the ease with which one may withdraw from the study.

The following steps will be taken in order to protect and/or mitigate risk:

- **Interview**: Before conducting research assessments, participants will be assured of confidentiality and told that they have the right to terminate the interview or to refuse to answer specific questions. Some interview questions may be considered sensitive and may cause emotional distress. It will be critical to make clear to participants that they can terminate the interview at any time for any reason. The interviewer will be trained to be sensitive to signs of participant discomfort and to suggest breaks where it seems appropriate.
- **Intervention**: Participation in the intervention may result in an initial increase in undesirable feelings. Interventionists will be trained to be aware of this possibility and how to help the

participant manage these feelings. In addition, participants are instructed to pace themselves through the intervention, and are encouraged to set their own limitations. Furthermore, the intervention is specifically geared towards dealing with such discomfort.

- **Confidentiality**: Loss of confidentiality is another possible risk. All information will be referenced to a participant identification number and will be sequestered in locked file cabinets in a locked office. The participant's ID number can be connected to the participant's name only through a single master file, password-protected, accessible only to senior research staff. We will protect all data files with passwords and lock any paper-based data collection instruments in cabinets. Risk of loss of confidentiality in conducting follow-ups will be avoided by having our interviewers never indicate to anyone other than the participant the purpose of the contact, unless the participant has given prior informed consent to do so.
- **Risk of ineffective intervention**: The risk of possible ineffective intervention will be minimized by the fact that study participants will continue with their current medication or other treatment for chronic pain and for depression. Study participants may choose to discontinue study participation at any time if they wish to enroll in non-study psychotherapy during the intervention phase

Given that all participants will have risk factors for suicidality (i.e., chronic pain and elevated depressive symptoms), some participants may experience suicide ideation or behavior in the course of study participation. Significant risk for suicide will be defined by PHQ-9 total score of 18 or greater, a score of greater than 0 on question 9 of PHQ-9 (both indicating suicide ideation or intent or behavior), OR the report of a desire or intent to hurt oneself to study staff. All staff members will be trained by Dr. Stein on the study's Suicide Ideation Protocol. Details on the procedural steps will be included in the study's Standard Operating Procedures (SOP), a copy of which all Research Assistants have with them at all times. The Suicide Ideation SOP details key warning signs and/or language of a participant with possible suicidal or homicidal thoughts and procedures for next steps. If a staff member encounters an individual who endorses suicide or homicide ideation, they will use the MSSI (Modified Scale for Suicidal Ideation) to ask a series of follow up questions to determine if a participant has a plan to hurt themselves or others, if they have tried to do so in the past, and if they have access to a specific method of self-harm. Following this brief discussion, the research member will immediately call a senior staff member to review the participant's responses and determine if immediate action is necessary. Each site will have at least two licensed clinicians identified to assist with study participants who endorse harming themselves or others. This individual will be called and/or paged and will reach out to the participant immediately for evaluation. When a clinician is asked to conduct an immediate evaluation, he or she will conduct a suicide risk assessment. The clinician will determine whether it is necessary to take immediate action to prevent the participant from causing harm to him/herself. If the participant is not in immediate danger of hurting him or herself, we will take the following actions. First, we will inform the patient about procedures for contacting emergency services should they find themselves at risk for self-harm. Second, with the patient's permission, we will contact their primary care physician or other clinician to inform them of the suicidality. We will urge the patient to make an appointment with that provider to discuss treatment options. Third, if the patient consents, we will speak with one of their family members to ensure that he/ she is aware of the seriousness of the patient's symptoms and the agreed-upon treatment plan. We will provide treatment referrals if the patient wishes. Regardless of outcome, suicide assessments are always documented in writing.

If a participant endorses suicide or homicide ideation over the phone, all procedures will remain the same, however, we first ask the participant where they are in case emergency services need to be called to their location. The research staff will keep the participant on the phone and conference in the study clinician to conduct the suicide risk assessment. Additionally, all participants will be given a brochure at enrollment with information about local resources for mental health services and suicide prevention.

6.2 Potential Benefits

From a societal standpoint, this research endeavor could lead to the incorporation of a theoretically-driven and effective behavioral health treatment for patients with pain and depression into OUD care. This would be the first large-scale study of behavioral health treatment for chronic pain in people with OUD. We believe that this treatment will lead to improved pain, depression, and OUD outcomes. The risks of suicide or homicide are inherent in this patient population. All participants may acquire an increased awareness of their connections between pain and depression, and how these connections may relate to their OUD care plan. Participants assigned to the Life Goals intervention may further benefit by developing pain and mood management skills. Participants assigned to the HE intervention may benefit by increasing their knowledge of general health issues. Given that the risks of participation are fairly low, the risks to participants are judged to be acceptable relative to the anticipated benefits.

6.3 Analysis of Risks in Relation to Benefits

The risks to participants are judged to be acceptable relative to the anticipated benefits. By participating in the clinical research project, participants may benefit from the intervention that they will receive. The potential benefits to others in the future and to the scientific community, and thus to society, are considerable, and the risk-benefit ratio is deemed favorable.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Between 18 and 65 years of age
- Have chronic pain, defined as pain duration for at least three months with a mean score of 4 or higher on the BPI Pain Interference Scale
- Pain severity of 4 or higher on a Numeric Rating Scale (0-10) indication "worst pain in the last week"
- If using an antidepressant, the dose must be stable for the previous 2 months
- Has received buprenorphine from current primary care provider for at least the last month
- Score of at least 4 on the PHQ-8 during prescreen and score of at least 4 on PHQ-9 during screening
- Gives informed consent to participate in the study

7.2 Subject Exclusion Criteria

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

- Expected surgery in the next 3 months

- Pain thought to be due to cancer
- Greater than or equal to 10 days of cocaine/crack/methamphetamine use in the past month
- Current mania or past year psychosis as determined via SCID (Strutured Clinical Interview for DSM) Modules A and B/C
- Lifetime diagnosis of schizophrenia or other chronic psychotic condition as determined by the study PI
- Planning to stop using buprenorphine in the next 6 months
- Headache/migraine is the only reported site of pain
- Pregnancy or planned pregnancy in the next 6 months
- Greater than 8 homeless nights in the past month
- Suicide ideation or behavior requiring immediate attention
- Not able to complete interviews in English
- Unable to provide names and contact information for at least two verifiable locator persons who will know where to find them in the future
- Greater than or equal to 45 days without a phone in the past 3 months/no reliable access to phone
- REMOTE ONLY: Does not have internet access or mailing address
- IF PASSIVE RECRUITMENT: Cannot confirm active buprenorphine prescription

8 Study Intervention

The TOPPS study will compare two groups: TOPPS intervention (Intervention condition) and Health Education (Control Condition). The intervention will last three months. All participants will participate in 6 intervention sessions with a trained Behavioral Health Specialist (BHS). For both TOPPS and HE participants, Session 1 will be a one-on-one conversation between the BHS and the participant. Session 1 can be completed in the same day as the baseline assessment or it can be completed on a different day either by phone or in-person. Sessions 2-6 may be conducted over the phone for both intervention groups but can also occur in-person, if necessary. Intervention sessions 2-6 will occur in order, the interventionists will not move on to the next session until the previous one has been completed. Participants will schedule intervention sessions separately with study staff based on BHS availability.

TOPPS*:*

TOPPS consists of three main components: (1) psychoeducation about pain, depression, opioid use, their interactions, and the maintaining role of avoidance; (2) coaching in being an informed, activated patient (based in part on the chronic care model and on approaches to self-management of chronic illness); and (3) behavioral activation to increase engagement in meaningful activities. Life Goals Behavioral Health Specialists (BHS) do not directly treat substance misuse/abuse, but they do assess substance use and support all efforts to attain or maintain sobriety as part of buprenorphine care and retention; these may become part of the patient's life goals. Life Goals BHSs describe their goal as helping patients to engage more in their life as a patient with chronic illness by reducing avoidance and increasing achievement of life goals. Consistent with an effort to engage patients, Life Goals will aim to involve an initial face-to-face meeting followed by regular phone meetings. In preliminary research, patients found this format to be convenient. The initial meeting includes the patient and the BHS. After each Life Goals session, with patient permission, the BHS mails or emails a copy of the clinical note to the patient. This note increases the contact between patient and BHS, serves as a reminder to patients about their goals, and

encourages the patient to be informed and activate in their own healthcare. Additionally, each participant is provided with a workbook that reviews the key elements of each treatment session and provides exercises for at-home practice of skills. Session 1 will last for 45 minutes. All following sessions will last for a maximum of 30 minutes. Sessions 1-6 will occur over the phone or in-person, if necessary.

Health Education:
The initial meeting includes the patient and the BHS to discuss nutrition. For the next 5 sessions, they choose from a menu of topics, including: a second session on nutrition; germs, colds and the flu; preventing cancer; diabetes; protecting your heart; getting a good night's sleep; complementary and alternative medicine; caffeine, or physical activity. This control condition was accepted by our participants in preliminary studies; it does not directly target functional impairment, and participants do not set tailored goals relating to their own values. Session 1 will last for 45 minutes. All following sessions will last for a maximum of 30 minutes. Sessions 1-6 will occur over the phone or in-person, if necessary.

9 Recruitment and Retention Procedures

9.1 Recruitment Procedures

Participants will be recruited from two sites: Boston Medical Center Office Based Addiction Treatment (OBAT) program and Stanley Street Treatment and Resources (SSTAR) in Fall River, Massachusetts, as well as through advertising and passive recruitment.

Potential participants recruited through OBAT and SSTAR will be recruited through letters mailed or emailed by a member of the research team, flyers given by clinic staff during the potential participant's scheduled medical appointment in the OBAT program or through SSTAR, or following RA introduction by a member of OBAT or SSTAR clinic staff. Potential participants may opt out from the study before eligibility screening occurs. Patients who do not opt out will be contacted (by phone or in person) by a member of the research team. Potential participants may also reach out to study staff directly based on response to advertisements or following passive recruitment (e.g. word-of-mouth, current participant referral, or flyer).

On initial approach, the RA will introduce the study, review the screening consent form and obtain verbal consent prior to administering the eligibility screening questionnaire. Recruitment data will be collected through REDCap. Patients who meet the initial eligibility requirements will be asked to schedule a telephone call or to meet in-person with a member of the research team to conduct the informed consent procedures, administer the post-written consent eligibility screener (to confirm eligibility and to link their screening data to identifiers), administer additional post-written consent screening measures (namely the PHQ-9 and the SCID Module A and Module BC, and confirm buprenorphine prescription for those recruited via advertisements or passive recruitment) and complete the baseline assessment, and if eligible, complete intervention procedures. All of these procedures may take place on the same day but are not required to occur on one day.

1. EHR/CDW Data Pull: Patient lists will be generated by the Electronic Health Record (EHR) data pull or Clinical Data Warehouse (CDW) and may include either:

> 1) Patients who, (1) currently receive buprenorphine, and (2) have an encounter with the OBAT clinic within the specified date range;

2) Or may include patients who, (1) currently receive buprenorphine, (2) have an encounter with the OBAT clinic within the specified date range, and (3) have at least one of the following listed in their medical record: pain diagnosis, depression diagnosis, or a prescription for an antidepressant.

Providers will be provided with the generate list of their patients to be screened either in person or via a note in the EHR, and will have the chance to remove patients from the list that they feel should not be approached. To minimize undue burden on potential participants and providers, research staff may access the electronic medical record to confirm eligibility by CDW criteria prior to adding potential participants to the provider lists. Research staff will mail or email individualized letters to potential participants using "opt-out" language, such that the potential participant must call the study phone number to avoid being contacted by research staff. This letter will be signed by and sent on behalf of the Medical Director or head nurse of the medication-assisted treatment program (in the case of SSTAR) or by the Medical Director (in the case of OBAT).

2. In-person Recruitment: Participants who have received an opt-out letter but cannot be reached by phone may be approached by study staff during their clinic appointment. Study staff will request approval from the potential participant's provider before approaching the participant. Study staff will provide the participant with information about the study and if the participant is interested and has time, complete screening procedures.

Participants may also be identified by clinic staff and may either be given a brochure with information about the study or be directly introduced to study staff (warm hand-off).

3. Passive Recruitment: Study staff may hang flyers advertising the study and study contact information. Study staff may advertise the study (e.g. via Google Ads, Reddit, Craigslist, StudyFinder, Facebook, Twitter, Suboxone-related websites/online forums, and paper flyers) or participants may be referred to the study by other means (e.g. enrolled participant referral). We have expanded passive recruitment via the service of BuildClinical. BuildClinical is a data-driven software platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. They utilize study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc., and redirect them to a study-specific landing page should they click it. Interested participants who reach out to study staff for more information (either by phone or in-person) will be screened for eligibility. RAs also have the option to send potentially eligible participants a private scheduling link using Microsoft Bookings for Me,a HIPAA-compliant Microsoft-based scheduling tool that integrates directly with BU (Boston University) Outlook emails and calendars. When potentially eligible participants fill out a pre-screening form from BuildClinical, RAs will reach out via text or email with the 15-minute phone screen scheduling link, and the participants will have the option to self-schedule a time on the research assistant's calendar. Participants would only be able to see the times the RA is available; no other details of the RA's calendar will be visible. RAs could also send this link to potentially eligible participants who filled out the BuildClinical screening form and we have not yet been able to get in contact with (before the implementation of Bookings With Me). Participants recruited via passive recruitment who report being on BUP (buprenorphine) will be asked to provide confirmation that they are actively receiving a buprenorphine prescription during screening measures after full consent. Following initial screening measures, if eligible and interested, potential participants will be informed they will need to provide proof of active BUP prescription at their next study appointment. Participants who report being on BUP during screening will provide confirmation through self-report. This will be confirmed through objective data. Verification of BUP can occur through the following:

1. Participant providing a pill bottle or image thereof that confirms the BUP prescription belongs to them. Study staff will review the pill bottle/image of pill bottle but will not retain any data from

the bottle; study staff will only report Y/N was buprenorphine prescription confirmed and the avenue by which it was confirmed.

2. Participant providing written script or image thereof that confirms the BUP prescription belongs to them. Study staff will review the script/image of script but will not retain any data from the script; study staff will only report Y/N was buprenorphine prescription confirmed and the avenue by which it was confirmed.

3. Participant providing description of injectable BUP receipt which can include: date, provider name, and dosage amount. Study staff will review responses with study PI(s) and Research Manager to confirm participant eligibility. This information will not be saved with the participant's screening data; study staff will only report Y/N was buprenorphine prescription confirmed and the avenue by which it was confirmed.

4. Verbal or written communication from MOUD (medications for opioid use disorder) prescriber or opioid treatment program after participant has signed 42 CFR Part 2 compliant ROI. Written communication will not be retained; study staff will only report Y/N was buprenorphine prescription confirmed and the avenue by which it was confirmed.

RA will simply mark, BUP prescription confirmed, Y/N and the route of confirmation in the screening form. The RA will not retain data beyond confirmation and route of confirmation.

If remote, participants will be asked to send a photo of options 1-2 via secure email or text message. For the transfer of sensitive BUP data, study staff will always attempt to request this data via BU's secure email service, DataMotion. Study staff will send an encrypted email to participants via DataMotion during screening measures after full consent. Participants will be instructed to create a username and password for DataMotion and respond with a photo of options 1 or 2. If the participant requests to send this photo via unencrypted email or text message, study staff will remind participants of the risks of sending sensitive data via unencrypted communication methods, as written in the Locator Form and make note in the Locator Form notes section of the participant's final choice in method of data transfer. If the participant chooses to send BUP confirmation data via unencrypted communication methods, study staff will advise participants to delete the message/image from their electronic devices. Once the BUP prescription is confirmed, this photo will be immediately deleted and wiped from memory by study staff.

If in person, participants will be asked to bring options 1 or 2 to their study appointment.

If receiving injectable BUP participants should be prepared to answer a series of questions regarding their injectable BUP, the answers of which will not be recorded by study staff.

If participants recruited via passive recruitment cannot confirm active BUP prescription, they will not be able to be enrolled in the study.

9.2 Retention Procedures

Maintaining a high follow-up rate will be essential to the successful completion of this study. Participants will take part in the following research assessments: baseline, 1-, 2- 3-, 6, 9-, and 12-month. Within each assessment period, there is an interview that is estimated to last between 60 and 120 minutes. To enhance participant retention, participants will receive compensation for each individual interview. Participants will receive compensation following assessment completion. The amount of compensation for assessment completion is based on the length of the assessment (larger

compensation for baseline and 3 month) and will increase incrementally throughout the course of the study to aid in study retention. The maximum total participants can earn for completing study interviews is $370 or $430 (for those who complete a 12-month interview).

To assist in maintaining high follow-up rates for study assessments, study staff will contact participants by phone, email, and text message to communicate about assessment reminders, scheduling, re-scheduling, etc.

Study staff will also mail out letters to hard-to-reach participants to remind them of their upcoming intervention sessions, if needed.

10 Screening Procedures

Potential participants will be recruited through letters mailed by a member of the research team, by flyers given by clinic staff during the potential participant's scheduled medical appointment in the OBAT program or through SSTAR, or following RA introduction by a member of OBAT or SSTAR clinic staff. Potential participants may also reach out to study staff directly based on response to advertisements or following passive recruitment (eg. word-of-mouth, current participant referral, or flyer). Potential participants may opt out from the study before eligibility screening occurs. Patients who do not opt out will be contacted (by phone or in person) by a member of the research team (see Recruitment section).

1. EHR/CDW Data Pull: Patient lists will be generated by Electronic Health Record or Clinical Data Warehouse and and may include either:
Patients who (1) currently receive buprenorphine, and (2) have an encounter with the OBAT clinic within the specified date range; Or may include patients who (1) currently receive buprenorphine, (2) have an encounter with the OBAT clinic within the specified date range, and (3) have at least one of the following listed in their medical record: pain diagnosis, depression diagnosis, or a prescription for an antidepressant.
Providers will be provided with the generate list of their patients to be screened either in person or via a note in the EHR, and will have the chance to remove patients from the list that they feel should not be approached. To minimize undue burden on potential participants and providers, research staff may access the electronic medical record to confirm eligibility by CDW criteria prior to adding potential participants to the provider lists. Research staff will mail or email individualized letters to potential participants using "opt-out" language, such that the potential participant must call the study phone number to avoid being contacted by research staff. This letter will be signed by and sent on behalf of the patient's provider (in the case of SSTAR) or by the Medical Director (in the case of OBAT).

2. In-person Recruitment: Participants who have received an opt-out letter but cannot be reached by phone may be approached by study staff during their clinic appointment. Study staff will request approval from the potential participant's provider before approaching the participant. Study staff will provide the participant with information about the study and if the participant is interested and has time, complete screening procedures.

Participants may also be identified by clinic staff and may either be given a brochure with information about the study or be directly introduced to study staff (warm hand-off).

3. Passive Recruitment: Study staff may hang flyers advertising the study and study contact information. Study staff may advertise the study (e.g. via Google Ads, Reddit, Craigslist, StudyFinder, Facebook, Twitter, Suboxone-related websites/online forums, and paper flyers) or participants may be referred to the study by other means (e.g. enrolled participant referral). The screening process for participants recruited via BuildClinical will be identical to those screened via passive recruitment (i.e., those who reach out to the study team upon seeing an advertisement on Craigslist), with the addition of the BuildClinical landing page and pre-screening form (BuildClinical Pre-Screening Questionnaire). Upon clicking on the advertisement, potential participants will be brought to the TOPPS study landing page built by BuildClinical, which provides basic information on the study and acts as a Brief Screening Agreement in this way. If the potential participant is interested in the study and would like to see if they are eligible, they would then click the link to the Pre-Screening Questionnaire. Research Assessors will be able to review participant's responses to the questionnaire and reach out to them if they are eligible based on the questions, which represent a subset of the questions on the full screener. From there, RAs would contact the potential participant, administer the approved Brief Screening Agreement, obtain verbal consent, and complete the TOPPS Screening Questionnaire, as usual.

Interested participants who reach out to study staff for more information (either by phone or in-person) will be screened for eligibility. Participants recruited via passive recruitment who report being on BUP will be asked to provide confirmation that they are actively receiving a BUP prescription during screening measures after full consent. Following initial screening measures, if eligible and interested, potential participants will be informed they will need to provide proof of active BUP prescription at their next study appointment. Participants who report being on BUP during screening will provide confirmation through self-report. This will be confirmed through objective data.
Verification of BUP can occur through the following:
•Participant providing a pill bottle or image thereof that confirms the BUP prescription belongs to them. Study staff will review the pill bottle/image of pill bottle but will not retain any data from the bottle; study staff will only report Y/N was buprenorphine prescription confirmed and the avenue by which it was confirmed.
•Participant providing written script or image thereof that confirms the BUP prescription belongs to them. Study staff will review the script/image of script but will not retain any data from the script; study staff will only report Y/N was buprenorphine prescription confirmed and the avenue by which it was confirmed.
•Participant providing description of injectable BUP receipt which can include: date, provider name, and dosage amount. Study staff will review responses with study PI(s) and Research Manager to confirm participant eligibility. This information will not be saved with the participant's screening data; study staff will only report Y/N was buprenorphine prescription confirmed and the avenue by which it was confirmed.
•Verbal or written communication from MOUD prescriber or opioid treatment program after participant has signed 42 CFR Part 2 compliant ROI. Written communication will not be retained; study staff will only report Y/N was buprenorphine prescription confirmed and the avenue by which it was confirmed. RA will simply mark, BUP prescription confirmed, Y/N and the route of confirmation in the screening form. The RA will not retain data beyond confirmation and route of confirmation.

If remote, participants will be asked to send a photo of options 1 or 2 via secure email or text message. For the transfer of sensitive BUP data, study staff will always attempt to request this data via BU's secure email service, DataMotion. Study staff will send an encrypted email to participants via DataMotion during screening measures after full consent. Participants will be instructed to create a

username and password for DataMotion and respond with a photo of options 1-2. If the participant requests to send this photo via unencrypted email or text message, study staff will remind participants of the risks of sending sensitive data via unencrypted communication methods, as written in the Locator Form and make note in the Locator Form notes section of the participant's final choice in method of data transfer. If the participant chooses to send BUP confirmation data via unencrypted communication methods, study staff will advise participants to delete the message/image from their electronic devices. Once confirmed, this photo will be immediately deleted and wiped from memory by study staff.

If in person, participants will be asked to bring options 1 or 2 to their study appointment.

If receiving injectable BUP participants should be prepared to answer a series of questions regarding their injectable BUP, the answers of which will not be recorded by study staff.

Participants can also choose to sign a release form to allow study staff to confirm BUP prescription with their current provider. If remote, this will be signed via REDCap.

If participants recruited via passive recruitment cannot confirm active BUP prescription, they will not be able to be enrolled in the study.

Patients who do not opt out will be contacted (by phone or in person) by a member of the research team. On initial approach, the RA will introduce the study, review the screening consent form and obtain verbal consent prior to administering the eligibility screening questionnaire. Screening data will be collected through REDCap. We will de-identify the data for all participants who are screened out of the study. Data for participants who remain enrolled in the study will also be de-identified. Patients who meet the initial eligibility requirements will be asked to schedule a telephone call or to meet in-person with a member of the research team to conduct the informed consent procedures, administer the eligibility screener (to confirm eligibility and to link their screening data to identifiers), administer additional screening measures (namely the PHQ-9 and the SCID Module A and Module B/C, and confirm BUP prescription for those recruited via advertisements or passive recruitment) and complete the baseline assessment, and if eligible, complete intervention procedures.

11 Consent Procedures

If the individual is willing to participate, the research assistant will administer informed consent (Written Consent Form) for study participation. The consent process will take place in a private space either at Boston University Medical Campus or SSTAR, or may occur electronically or over the phone with a witness. A Written Consent Form will be given to potential participants prior to consent either in person or by mail, secure email, or REDCap, if remote. The potential participant will be given time to read the study consent form and fact sheet prior to consent. Participants will not be consented to the study if they have not yet received a consent form from study staff. The forms will be reviewed with the potential participant either in person or by an audio only phone call, Zoom teleconferencing software, or BU Teams communications platform. There will be time for the potential participant to ask questions prior to consenting to study participation. The potential participant may postpone consent if they would like more time to consider study participation prior to consent.

The informed consent form explains the purpose of the research, the nature and duration of the study, that the study is voluntary, that a participant may withdraw consent at any time during the study,

potential disadvantages of participation, alternatives to participation, and procedures for safeguarding confidentiality. To ensure informed consent comprehension RAs will utilize the Informed Consent Checklist and Teach Back. Participants will be given a copy of their signed consent when in person or sent an electronic PDF of their signed consent via REDCap or secure email, if possible.

If in person, participants will provide consent by signing a physical consent form. If the participant is a limited or non-reader, an impartial witness will also be present during consent and will sign confirming the consent process was completed appropriately.

If remote, consent may occur electronically via REDCap - this can occur via the e-consent method or the remote signature consent method. Participants who provide consent using the e-consent method will be directed to sign the consent form electronically via REDCap. Participants who provide consent using the remote signature method will direct a witness taking part in the consent discussion to sign on behalf of the participant. If a participant is a limited- or non-reader the witness will be impartial and will NOT be a member of the study team. The witness will be present for the entire consent discussion. For participants who are NOT limited- and non-readers but who are unable to engage in e-consent, the witness can be a member of the study team since there is no requirement for an impartial witness in this study but may also be an impartial witness if a study team member is unavailable. The witness will be present for the end of the consent discussion when the signature is applied to the consent form but can also be present for the entire consent discussion, if they so choose. The participant will be reminded to apply their signature or mark on their copy of the consent form.

If a participant is consented via the remote signature consent process, meaning they cannot electronically sign the consent form, the witness signature will suffice as signature via proxy. If the participant completes an assessment in person in the future, staff will make every effort to have the participant physically sign the witness signed consent form. The form signed would be the same consent form version they were originally consented with using the remote signature consent process. The participant will be instructed to sign with the date of original consent and a note to file will be created that indicates the signature was formally applied at an in-person visit. If staff are unable to get a participant signature during an in-person assessment for any reason, consent remains intact.

For participants who are limited- and non-readers but do have access to internet, we will attempt to obtain an electronic signature via REDCap if there is someone present with them who can read and help them sign (e.g., spouse). If no such person is available, then we will utilize the remote signature consent process as described above.

12 Study Procedures

See the Appendix for the schedule of events.

Baseline and Follow-Up Assessments:

The baseline visit with take place at BMC (Boston Medical Center) or SSTAR if possible, but may also be conducted by telephone. At consent/baseline, research staff will collect participants' contact information, including phone number(s), mailing address, and e-mail address if applicable. Staff will also collect the phone numbers for two alternate contacts that they may call if unable to reach the participant. Research staff will keep in regular contact with participants by phone or by text message,

and participants will be encouraged to contact the study team if they change their contact information. If participants report that they plan to enter a temporary residence, shelter, or facility, they will be asked to fill out a form authorizing the facility to release their admission status and/or contact information to study staff. If remote, this form can be sent electronically (REDCap/Docusign). If this is not possible, we will wait to complete this form until assessments can occur in person. If a participant becomes incarcerated during study participation, research staff will not complete assessments with them while incarcerated but will monitor release date to re-engage the participant upon release. Participants will be compensated for each assessment and FitBit Inspire return and we will attempt to contact participants for all assessments regardless of whether they remain in the assigned treatment (see Table 1). Compensation can include Visa® gift cards or electronic gift cards. We may also cover local transportation costs and offer offsite or phone assessments to increase convenience for participants.

The baseline interview is administered by trained RAs and takes approximately two hours to complete. A list of assessment measures is included in the Appendix. Participants are mailed or emailed assessment scales prior to the scheduled call. Participants' eligibility is reassessed at this time, and if they are found to be no longer eligible, they are compensated and thanked for their time. Eligible participants are administered the assessment and are randomized upon completion of the interview.

Assessments will be conducted in-person and over the phone. Baseline assessments will take a maximum of one hour to complete (expected 45 minutes). Follow-up assessments will take one half hour to complete. Assessments will be directly entered into REDCap when possible, however paper versions will be available if an assessment is conducted off-site. Participants will receive compensation following assessment completion. The amount of compensation for assessment completion is based on the length of the assessment (larger compensation for baseline and 3 month) and will increase incrementally throughout the course of the study to aid in study retention.

FitBit Inspire Tracking:

All study participants will receive a FitBit Inspire to collect the number of steps taken per day. Participants will not be given access to the FitBit web-based or smartphone applications. Participants will be asked to wear the FitBit continuously for 7 days after baseline and return the FitBit either in person or via pre-paid envelopes. Participants will be compensated for returning their FitBit Inspire.

Intervention Sessions:

<u>TOPPS</u>

The TOPPS intervention consists of 3 main components: 1) psychoeducation about pain, depression, opioid use, their interactions, and the role of avoidance; 2) coaching in how to be an informed, activated patient; and 3) values-based, behavioral activation, to increase engagement in meaningful activities. Throughout the intervention, three core messages are discussed with participants: 1) Everyone experiences sadness and pain. Just because something hurts, it doesn't mean it's dangerous; 2) It is natural to want to be comfortable. Nearly everyone wants to avoid sadness and pain; and 3) Sometimes working towards important goals is worth it, even if it temporarily increases pain or discomfort. Participants are informed that the primary goal of this intervention is not take away all of their pain, but rather to help them 'live the life they want, as comfortably as possible".

There are a total of six phone-based sessions. The first two sessions last approximately 50 min each; the remaining four sessions are approximately 30 min in duration. Session 1 is focused on a) rapport

building; b) validating the participant's experience with both physical and emotional pain; c) psychoeducation about the differences between acute and chronic pain, the relationship between pain and depression, and the role of avoidance in maintaining a cycle of pain, depression, and substance use; d) values clarification; and e) beginning to set long-term goals in service of the participant's values. During values clarification, interventionists work with participants to help them identify the things that matter most to them (e.g., family, helping others, community, friendship, health, etc.) and to understand the ways in which their aspirations have been altered or unfulfilled due to their pain and substance use. Long-term goals are set collaboratively, with the interventionist assisting the participant to identify things they would like to achieve in life, in service of their values, and which are manageable with whatever restrictions their pain and substance use history may have caused.

During session 2, identification of long-term goals is completed. Interventionists then teach SMART goal setting, helping patients to make Specific, Measurable, Achievable, Relevant, and Time-bound short-term goals as the steps needed to take to get to achieve their long-term goals. For example, the participant sets a goal to spend 30 min, on Monday and Wednesday evening, using his laptop to research potential volunteer opportunities in his area. He also set goals to text one of his old friends to say hello and that he felt badly he been out of touch for so long and to begin taking short, 10-min walks, 3 days a week.

Sessions three – six are focused on review of previous short-term goal progress, setting new short-term goals, and establishing goal-setting skills to be used by the participant independently in the future. Time-based pacing, a technique common to behavioral treatments for chronic pain in which participants identify the amount of time they can perform a task without an increase in pain and then plan to break the activity into time blocked segments of this duration, is also taught. The goal of time-based pacing is to help ensure that participants don't take on too much physical activity all at once in pursuing their short-term goals leading to increases in pain and feeling unable to continue working towards their goals. Skills to be a more active and informed participant in care of their chronic conditions (pain, substance use) are also taught, such as making a list of questions for their healthcare providers keeping a calendar with all their appointments listed, etc.

The intervention is delivered by Behavioral Health Specialists (BHSs), who have backgrounds in mental health counseling (i.e., clinical psychology graduate students, MSWs, and PhD psychologists). Upon randomization, each participant assigned to the intervention is assigned a specific BHS with whom they meet for the duration of the intervention. The first session is scheduled to take place within two weeks of the baseline assessment. All sessions are audio-recorded. At each session, the BHS administers the Patient Health Questionnaire-2 (PHQ-2), a pain questionnaire, and buprenorphine adherence questions.

Sessions 1 and 2, and sessions 2 and 3 are ideally scheduled to take place within one week of each other. Remaining sessions are scheduled approximately two weeks apart. To allow for flexibility, participants have 3 months to complete all six sessions.

<u>Control Condition- Health Education</u>

Participants randomized to the control HE condition are offered six sessions led by the BHSs. As with TOPPS, each participant is assigned one BHS who delivers all their sessions. The same pool of BHSs provides TOPPS and HE. TOPPS research assistants have also been trained to deliver HE if BHS caseload capacity is low. RAs do not administer assessments to any participants to whom they deliver HE. Delivery, timing, and duration of the HE sessions are identical to the TOPPS intervention condition. The first health education session is titled "What to Eat." Participants then select five additional topics, one

for each of the remaining sessions. Topics include, "What Not to Eat," "Colds, Germs, and Flu," "Preventing Cancer," "Diabetes," "Protecting your heart," "Getting a Good Night's Sleep," "Complementary and Alternative Medicine (CAM)," "Caffeine," and "Physical Activity." At each session, the Behavioral Health Specialists also administer the same mood, pain, and buprenorphine adherence questionnaires as in the TOPPS condition.

Treatment Fidelity and Training

Fidelity checklists are used for each session (e.g., rapport building, completion of planned agendas, content), including measurement of potential contamination across interventions. Investigator (RW, Risa Weisberg) and one or more additional PhD-level psychologists rate 50% of the initial sessions of BHSs in the training phase and then 10% of all other sessions. Fidelity ratings are used to measure adherence to the interventions and to provide feedback and education to BHSs and promote discussion in biweekly supervision sessions.

Prior to beginning the first intervention case, behavioral health specialists participate in training that involved the following elements: a) individually reviewing the intervention manuals; b) three hours of training with one of the study investigators (RW), in which the rationale and background science for the interventions are discussed, the session structure and primary goals of each session are reviewed, and the main therapeutic content of each intervention are reviewed with examples and/or role-playing provided on how to deliver these elements; c) listening to recorded example cases of each intervention; and d) a follow-up meeting with RW to answer any questions raised when reviewing the example cases.

Follow Up Assessments

Follow up interviews are conducted by trained RAs at 1-, 2-, 3-, 4-, 6-,9-, and 12-months post-enrollment. All sections of the assessment are interviewer-administered and entered directly into REDCap. Participants are compensated up to $430 in gift cards throughout the study. Participants receive compensation at the end of each baseline or follow-up assessment.

13 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

13.1 Definitions for Safety Assessment

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;

(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol (Institutional Review Board), any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

13.2 Safety Review

Both the risks listed in Section 4.1 and unknown risks will be monitored as follows: Adverse events and serious adverse events, including but not limited to psychological stress or discomfort form research interviews, and loss of confidentiality, will be reported by study staff (e.g., research assistants, project manager, PIs, etc) and monitored by the principal investigator. SAEs will be evaluated within 48 hours of the study staff and team becoming aware of the event for severity, seriousness, and relatedness. We have procedures and reminders in place for study staff to notify the principal investigator when an AE or SAE is reported. Additionally, we will send a yearly report to our Data Safety Monitoring Board (DSMB) who will monitor and review AEs and SAEs. The DSMB will review rates of adverse events to determine any changes in participant risk, recruitment and retention, and participant drop out, and will make appropriate recommendations for changes in protocol, which will be submitted to the Boston University Medical Campus IRB for review. A brief report will be generated yearly for the study record and forwarded to the Boston University Medical Campus IRB.

13.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus will be reported to the BMC/BU Medical Campus IRB within 7 days of the investigator learning of the event.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

13.4 Stopping Rules

The study has no pre-defined stopping rules.

14 Data Handling and Record Keeping

14.1 Confidentiality

All data will be collected for research purposes and all records will be stored in locked filing cabinets or password protected computers accessible only to research staff. Research data will be collected and stored using subject IDs rather than participant names or other direct identifiers such as medical record number. Any paper copies will be kept in locked offices. Electronic files containing any identifiable information (such as the study key) will be password protected and only research staff will have access to the password. The study key will be kept separate from the study data (assessments and audio recordings). Files containing audio-recordings of participants will be password protected as well.

Study data collected by research study staff during research interviews in private locations. Study data collected by research study staff includes baseline and follow-up interview data. All research interview data will be entered into REDCap, managed by BEDAC. REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails, and data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium and was initiated at Vanderbilt University. The REDCap is hosted on a computer network exploitation -based server. Network transmissions (data entry, survey submission, web browsing, etc.) in REDCap are protected via Secure Sockets Layer (SSL) encryption. Access to REDCap can be restricted at different levels (e.g., research assistant, PI, and Co-Investigators). Exported data from REDCap will be stored on the Boston University Medical Campus' secure password-protected server.

Audio-recordings of intervention sessions with participants will be uploaded and stored on a secure, HIPAA compliant server (e.g., DropBox, Box.com, SharePoint, etc). A study ID will be used to identify the recordings. They are not connected with the primary study database in any way.

14.2 Study Documentation, Source Data, and Case Report Forms (CRFs)

Data sources in the study include pre-screening data collected via BuildClinical, the phone screening data, baseline, 1, 2-, 3-, 5-, 6-, 9- and 12-month assessment data to be collected via phone or in-person and input into REDCap by study staff, medical record data, and, audio-recordings.

Screening information collected via BuildClinical will be housed securely in BuildClinical's online platform. Screening information on potentially eligible participants collected by BU study staff will be housed securely in REDCap.

The phone screen and study baseline and follow-up interview data will be collected verbally from the participant to study staff over the phone, and directly entered by research staff into REDCap case report forms, and stored electronically in REDcap. Information collected during the phone screening is collected to determine eligibility for the study. Research interviews will collect information on demographic variables, health and medical status, symptoms of anxiety and depression, pain, recent medical appointments, current medications, knowledge of opioids, pain treatments, physical activity, substance use, psychosocial functioning, experience of discrimination, satisfaction with the intervention, and more. Data collected at the follow up time points are to understand change over time, especially after the intervention period.

RAs conducted medical chart reviews from participants who were recruited from the two primary care, office-based addiction treatment (OBAT) buprenorphine clinics in New England to collect data on buprenorphine retention at 6- and 12-months post-enrollment.

Corrections on data collection forms: If any entry error has been made to hardcopy data collection forms, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All such changes will be initialed and dated. There will be no erasures or white-out on CRFs. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialed and dated.

14.3 Study Records Retention

All study records (e.g., informed consent, REDCap survey records, intervention session recordings, etc.) from this trial will be retained for a minimum of seven years after the study is completed per Boston Medical Center and Boston University requirements. Data stored in REDCap will be managed and retained by study staff. Hard copy documents will be stored in locked filing cabinets. After the seven years of required data retention, the study PI will determine when the information can be destroyed.

15 Statistical Plan

15.1 Study Hypotheses

1. Participants in the TOPPS intervention, compared to Health Education, will report less pain interference and pain severity over the 3-month treatment phase.

2. Participants in the TOPPS intervention, compared to Health Education, will report fewer depressive symptoms over the 3-month treatment phase.
3. The TOPPS intervention, compared to HE, will result in sustained improvements in pain interference, pain severity, depressive symptoms and buprenorphine treatment retention over the study period.

Examining mechanisms by which TOPPS may reduce pain interference. Proposed mechanisms include: 1) (increased) steps per day (as a measure of general physical activity level); 2) (increased) activities engagement; 3) (decreased) avoidance of meaningful life activities; and 4) (decreased) fear of pain.

15.2 Sample Size Determination

We plan to recruit 125 subjects to each study condition. Based on an attrition rate of 20% we anticipate having approximately 100 participants per condition available for analysis. Our primary power calculations are based on Aim 1. Based on the literature [17-19], we determined that a minimally significant difference between treatment groups on outcomes would be a standardized mean difference (SMD) of at least 0.4 at 3 months. Assuming $\alpha/2 = 0.05$, we need 99 subjects per arm to detect an SMD of 0.4 with $1-\beta = 0.8$. Thus, the proposed design has sufficient power to detect small-moderate effects for Aims 1 and 2.

15.3 Statistical Methods

We will present descriptive statistics. Random effects logistic regression will be used to determine if treatment condition, demographic characteristics, or baseline outcome measures predict study attrition. Any variables that significantly ($p < .10$) predict study attrition will be included in multiple imputation models and as covariates in multivariate models testing the effects of intervention. Graphical methods will be used to evaluate the distributions of outcome variables, examine model residuals, describe change in outcomes over time, and guide the specification generalized linear mixed models testing intervention effects. A 2-tailed probability of Type I error < 0.05 will be used for all null hypothesis tests. Missing data due to participant attrition and item non-response is inevitable. We will conduct intent-to-treat analysis using multiple imputation by chained equation (MICE) to generate fully populated data sets [20]. More specifically we will use the mi impute and mi estimate facilities in Stata 17 to generate and analyze the fully populated data files [21]. The number of imputed data sets will be determined by using the how many imputations procedure [22]. MICE is a flexible tool that allows imputing values for outcomes with a range of distributions (e.g., continuous, dichotomous, count, etc.). MICE assume data are missing at random (MAR) (e.g., missing is random conditional on variables in the imputation model). Variables used in the imputation models will include treatment assignment, all observed instances of the outcome being imputed, and any additional baseline variables found to significantly ($p < .10$) predict subject attrition using mixed-effects logistic regression. Including baseline predictors of attrition supports the MAR assumption.

The BPI, the VAS pain severity scales (worst and average in last week), and the PHQ-9 will be administered at baseline and at all follow-up assessments. The effect of intervention on pain interference (BPI-I), pain severity, and depressive symptoms during the 3-month treatment phase will be evaluated in a generalized linear mixed model framework using the fully populated data sets generated by MICE. Models will include baseline pain and PHQ-9 depression measures as covariates. All available panel data will be included in the model to support the efficiency of estimation. Time specific estimates

of treatment effects (e.g., the effect of treatment at 3-months) can be obtained by including the treatment by categorical (indicator variables) time interaction term. We plan to use the contrast and mimrgns post-estimation commands in Stata to recover relevant parameter estimates and test statistics. More specifically, a Wald χ2-test will be used to test the simple main effect of treatment at end of treatment. Additionally, we will generate graphs plotting the estimated average marginal means to facilitate substantive interpretation of results. Parallel methods will be used to evaluate the sustained effect of treatment post end-of-treatment (4-, 6-, 9-, and 12- months). Wald χ2-tests will again be used to test the simple main effects of treatment at post end-of-treatment assessments to determine if intervention effects are sustained over time.

The Cox proportional hazards model will be used to test the hypothesis that participants randomized to TOPPS will have higher buprenorphine treatment retention than persons randomized to HE. The outcome will be operationalized as self-reported continuous treatment since the prior interview at the time point assessed.

We will use Mplus 7 [23] to specify and estimate structural equation models (SEM) testing the hypothesis that decreased avoidance, and fear of pain mediate the relationship between intervention and pain interference and severity.

Additional baseline covariates will include ratings of pain severity, pain interference, and depression. As recommended by MacKinnon et al. [24], the statistical significance of the indirect effect will be assessed using bias-corrected bootstrapped standard errors. Significant indirect effects are consistent with the hypothesis that change in the purported mechanisms mediates the effect of intervention on outcome.

16 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH (International Council for Harmonization) Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB / Name of IRB of record for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. A copy of the initial IRB approval letter will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

17 Literature References

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18 Appendix

Schedule of Events

Table 1. Schedule of Study Measures

Measure	Description	Baseline	Sessions	Follow-Up Assessment (Months)						
				1	2	3	4	6	9	12
Sociodemographics Baseline	Demographic questions, including age and incarceration history	X								
Sociodemographics Follow-up	Demographic questions,	X		X	X	X	X	X	X	X

	including places slept									
PHQ-9[1]	Measure of severity of depression	X	X	X	X	X	X	X	X	X
BPI[2]	Ratings of pain severity and interference	X	X	X	X	X	X	x	X	X
Pain Experiences[3]	Time ratings of least severe pain	X		X	X	X	X	X	X	X
BADS[4]	Measure of behavioral activation of depression	X		X	X	X	X	X	X	X
Buprenorphine and Pain - Baseline	Measures of how buprenorphine helps with pain	X								
GAD-7[5]	Measure of severity of anxiety	X		X	X	X	X	X	X	X
TSR – Baseline[6]	Compiling a list of medical appointments in the past 3 months	X								
TSR- Follow-Up[6]	Compiling a list of medical appointments since last follow-up			X	X	X	X	X	X	X
TRAQ[7]	Compiling a list of current medications	X		X	X	X	X	X	X	X
Knowledge Questionnaire	Assess patient knowledge of opioids	X								
Pain Treatment Questionnaire[8]	Endorsements of pain treatments	X		X	X	X	X	X	X	X

	used and ranking of their helpfulness									
IPAQ[9]	Measure of physical activities in the past 7 days	X		X	X	X	X	X	X	X
CPAQ[10]	Assess acceptance of chronic pain	X		X	X	X	X	X	X	X
PASS[11]	Assess anxiety around pain	X		X	X	X	X	X	X	X
PROMIS Global Health[12]	Assess general domains of health and functions	X		X	X	X	X	X	X	X
ASI – Baseline[13]	Compile lifetime use of drugs and in the last 30 days	X								
ASI – Follow-up[13]	Compile use of drugs in the last 30 days			X	X	X	X	X	X	X
Nicotine[14]	Determine cigarette use and how often	X								
DIS[15]	Assessing Pain sensitivity	X				X		X		X
Perceived Control Scale[16]	Assessing sense of agency	X				X		X		X
CPV-I[17]	Determine values and success living according to those values	X		X	X	X	X	X	X	X
Experience of Discrimination[18]	Determine history of discrimination based on identity	X								

Buprenorphine and Pain – Follow-up	Assessing buprenorphine effectiveness with pain			X	X	X	X	X	X	X
Patient Global Impression of Change[19]	Assess impacts of study on their pain and sadness			X	X	X	X	X	X	X
CSQ-8[20]	Assess satisfaction with the intervention in general					X				
Patient Satisfaction[21]	Assess satisfaction with specific aspects of the intervention					X				
CEQ[22]	Assess effectiveness of intervention after Session 1	X								
Buprenorphine Adherence	Assess current use of buprenorphine		X							

[1]Patient Health Questionnaire-9 and -2 (PHQ-9, -2), [2]Brief Pain Inventory (BPI), [3]Pain Experience, [4]Behavioral Activation for Depression Scale (BADS), [7]GAD-7 (General Anxiety Disorder-7), [6]Treatment Services Review (TSR), [7]Transition Readiness Assessment Questionnaire (TRAQ), [8]Pain Treatment Questionnaire, [9]International Physical Activity Questionnaire (IPAQ) , [10]Chronic Pain Acceptance Questionnaire (CPAQ), [11]Pain Anxiety Symptom Scale (PASS), [12]Patient-Recorded Outcomes Measure Information System (PROMIS) Global Health, [13]Addiction Severity Index (ASI), [14]The Fagerström Test for Nicotine Dependence (Nicotine), [15]Discomfort Intolerance Scale (DIS), [16]Perceived Control Scale, [17]Chronic Pain Value Inventory (CPV-I), [18]Experience of Discrimination, [19]Patient Global Impression of Change, [20]Client Satisfaction Questionnaire-8 (CSQ-8), [21]Patient Satisfaction, [22]Credibility/Expectancy Questionnaire (CEQ)

Table 2. Intervention Topics by Session

Session Number	Week Number	Contents
Session 1	Week 1	• Introduction to TOPPS intervention

		• Elicit history of participants' opioid use, recovery/buprenorphine treatment, pain, and depression, including an understanding of the participants' current and planned buprenorphine treatment and any medical treatment for pain and/or depression • Explain the role of avoidance • Values clarification • Begin to explore participants' long-term goals • Describe treatment and enhance motivation for the intervention • Homework: participant is asked to continue identification of long-term goals and think about what is important in their life
Session 2	Week 2	• Psychoeducation about core messages of TOPPS • Pain and discomfort (e.g., sad feelings) are not dangerous in and of themselves • Avoidance is a natural response to emotional and physical pain • Pain and discomfort may be necessary to achieve important life goals • Complete long-term goal setting. • Teach SMART goals • Set short-term, SMART goals corresponding to long- term goals, for the next 2 weeks.
Session 3	Week 4	• Review core messages • Review of short-term goals set at session 2 and any barriers to meeting these goals • Discussion of time-based pacing • Setting a short-term goal to apply pacing to physically active task (e.g., walking, cleaning) • Setting of short-term goals corresponding to long-term goals for the following 2 weeks
Session 4	Week 6	• Review core messages • Discussion of short-term goals set at previous meeting, and barriers to meeting these goals • Introduce concept of disease self-management and being an activated, informed patient. This includes discussions

		of medication adherence, communication with provider, and making choices about one's own care. • Setting of a goal that will help the participant to be more active in the management of their chronic conditions • Setting of short-term goals corresponding to long-term goals for the following 2 weeks
Session 5	Week 8	• Discussion of short-term goals set at previous meeting, and barriers to meeting these goals • Setting of short-term goals corresponding to long-term goals for the following 2 weeks • Identification of accomplishments made during the course of the intervention • Planning for the participant to continue this work on their own
Session 6	Week 11	• Discussion of short-term goals set at previous meeting, and barriers to meeting these goals • Plan for how participant will continue to work towards long-term goals after end of therapy