Distress tolerance and benzodiazepine discontinuation in opioid agonist therapy, Phase 2
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1 List of Abbreviations

Abbreviation	Abbreviation definition
BZD	Benzodiazepine
OAT	Opioid agonist therapy
SUD	Substance use disorder
DT	Distress tolerance
DT-BD	Distress Tolerance – Benzodiazepine Discontinuation
ACT	Acceptance and commitment therapy
BU	Boston University
BMC	Boston Medical Center
BHC	Behavioral Health Clinic
OBAT	Office Based Addiction Treatment
RA	Research assistant

2 Protocol Summary

Title:	Distress tolerance and benzodiazepine discontinuation in opioid agonist therapy (OAT), Phase 2
Population:	4 individuals receiving OAT who are regularly using benzodiazepines and are interested in discontinuing benzodiazepine use
Intervention:	This study conducts a 13-week Distress Tolerance – Benzodiazepine Discontinuation (DT-BD) psychosocial intervention paired with benzodiazepine taper with the aim of assisting individuals receiving OAT discontinue benzodiazepine use. This psychosocial treatment intervention uses a combination of interoceptive exposure therapy and elements of acceptance and commitment therapy (ACT) to assist individuals in tolerating benzodiazepine withdrawal symptoms and teaching skills to prevent relapse to benzodiazepine use. It will also provide psychoeducation about benzodiazepine use in OAT.
Objectives:	Primary Objective: To pilot the DT-BD intervention in OAT patients discontinuing BZD use and assessing the strengths and limitations of the intervention.
Design/Methodology:	Implementation study, 13 weeks, 14 visits (1 baseline assessment + 13 study visits)
Total Study Duration:	Approximately 1 year
Subject Participation Duration:	Approximately 3 hours for baseline assessment, 30 minutes for each physician visit (13 physician visits) and 60 minutes for each therapy visit (9 therapy visits)

3 Background/Rationale & Purpose

3.1 Background Information

The use of benzodiazepines (BZDs) among opioid agonist treatment (OAT) patients has been associated with lower treatment retention[1], use of cocaine[2], and overdose mortality[3,4]. As such, there is great concern that BZD use makes OAT less safe and less effective. BZD use is common among OAT patients, varies by region and OAT type, and ranges from 13-74% among methadone patients and 20-43% among buprenorphine patients[3,5-7]. The most common motivations for BZD use in opioid users are to manage anxiety, to get high, and to manage sleep[8-11]. Because BZD use among OAT patients is often felt to be therapeutic, motivation to discontinue BZDs may be expected to be low. Yet when OAT patients who were using BZDs were asked if they would consider reducing or stopping BZD use, 40% reported they would[10].

Given the high prevalence of BZD use and its negative consequences in the OAT population, there has been surprisingly little work investigating strategies to discontinue BZD use in this group. Efficacious strategies to reduce long-term regular BZD use typically involve a gradual BZD taper, but more than half of patients do not tolerate the withdrawal period and approximately half of those that do, relapse within a month[12,13]. Augmenting the BZD taper with a psychosocial intervention is more effective than a taper alone in general population studies[14-16].

The standard of care for BZD discontinuation typically involves only a gradual BZD taper that can last from 4-16 weeks, and sometimes longer. Research supports augmenting the taper with a psychosocial intervention such as relaxation therapy (RT) or cognitive behavioral therapy (CBT) for benzodiazepine discontinuation but neither are typically offered in most settings, including at Boston Medical Center. This is often because of unavailability of evidence-based psychosocial interventions in many settings where patients are tapered off of BZDs. Other non-BZD pharmacological treatments are sometimes given such as antidepressants and non-hypnotic benzodiazepines to treat anxiety and insomnia symptoms brought on by the BZD taper.

Regarding the psychosocial intervention, little is known about which type of approach might be most effective in assisting OAT patients to discontinue BZDs. Two trials have tested a psychosocial intervention aimed at assisting BZD discontinuation which have explicitly included substance use disorder (SUD) patients[17,18], one of which was in a group of methadone maintenance patients[18]. Both tested a traditional cognitive behavioral approach and neither was effective in reducing BZD use compared to control. One approach that may be more effective involves improving their Distress Tolerance (DT), defined as an individual's perceived ability to experience and endure negative emotional and physical states. DT-based approaches, which typically involve a combination of exposure therapy and Acceptance and Commitment Therapy (ACT)[19-22], have increased abstinence in smokers[23] and improved DT in SUD patients[21]. ACT aims to elicit acceptance of negative thoughts, feelings, and sensations that are interfering with the ability to behave in a way that is consistent with one's values. Additionally, use of exposure therapy, particularly interoceptive exposure (exposure to somatic sensations of anxiety), improves BZD discontinuation in panic disorder patients[24,25]. Furthermore, ACT has been found to be effective for treatment of anxiety disorders[26] and is a promising intervention for relapse prevention in SUD patients[27] and insomnia[28,29], the three most common motivations for BZD use among OAT patients (anxiety, euphoria, sleep). Thus an approach involving interoceptive exposure and ACT may help patients tolerate BZD withdrawal symptoms and the underlying anxiety, BZD cravings, and insomnia that led to the initial BZD use by facilitating acceptance of the negative thoughts, feelings and sensations caused by these conditions and increasing engagement in values-oriented behaviors.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

3.2 Rationale and Purpose

The rationale for this line of research is that a DT-focused approach may help teach OAT patients who use BZDs the skills to improve their ability to tolerate the distress from BZD withdrawal symptoms and the symptoms that lead to BZD relapse (e.g. anxiety, cravings). The overall goal of this line of research is to develop a DT-based intervention in order to help OAT patients who use BZDs to improve their distress tolerance and thereby 1) increase likelihood of BZD discontinuation and 2) decrease risk of later relapse to BZD use.

The goal of this proposed study is to pilot test a Distress Tolerance – Benzodiazepine Discontinuation (DT-BD) intervention for OAT patients using BZDs, and to assess the applicability and feasibility of this intervention through treatment retention and qualitative interviews of 4 participants receiving OAT who regularly use BZDs. Participants will be interviewed to assess strengths and limitations of intervention. Data from the interviews will be used to refine the intervention condition.

4 Objectives

4.1 Study Objectives

Primary Objective: We aim to pilot the DT-BD intervention in patients currently receiving OAT who regularly use BZDs, in order to assess feasibility of the intervention and assess strengths and limitations of the DT-BD intervention. Our primary goal of this pilot study is to gather data in order to revise the intervention conditions so that we can test these conditions in a later randomized controlled trial.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

This study is a pilot study of the DT-BD intervention with the aim of assessing its strengths and limitations. Thus, the primary outcome is the acceptability and feasibility of the interventions assessed by qualitative interviews of the participants. During and at completion of the intervention, participants will be asked to provide extensive feedback on the content of the intervention, method of delivery, and structure.

4.2.2 Secondary Outcome Measures

The study's secondary outcome measures include completion of intervention, BZD use by urine drug tests and self-report, use of illicit drugs or alcohol by urine drug test and self-report, BZD withdrawal symptoms, anxiety and depression symptoms, sleep quality, and distress tolerance measures.

5 Study Design

This is a pilot clinical trial of the DT-BD intervention, which is an adjunctive psychosocial intervention in people seeking to discontinue BZD use. The study population will consist of outpatients receiving OAT for opioid use disorder who are also using BZDs regularly. All participants will receive the same BZD discontinuation protocol. This discontinuation protocol, or taper, is a usual clinical care benzodiazepine taper. We are piloting the DT-BD intervention as it has never been utilized in BZD discontinuation trials. The intervention consists of 14 study visits: the first visit consists of the baseline assessment and the first therapy visit, 4 subsequent weekly therapy visits, then a 9-week BZD taper which includes therapy visits (see Study Intervention section). Some participants may be prescribed non-benzodiazepine medications to treat the underlying conditions for which they were using BZDs [e.g. selective serotonin reuptake inhibitors (SSRI) for anxiety or hypnotics for insomnia] as per standard clinical care. Data collection will occur starting at the baseline assessment.

6 Potential Risks and Benefits

6.1 Risks

Participants will be carefully screened at the beginning and closely monitored during the study procedures. Eligible individuals will be informed of each study procedure and the associated potential risks. Participants will be informed about the risks associated with the study itself, as well as the risks involved with the benzodiazepine taper. Participants will be informed that risks involved with the taper are happening as a part of their clinical care and not for research purposes. Potential risks will include:

a. **Subjective discomfort**. It is possible that a specific focus on participants' BZD use and other drug use behaviors could produce some distress. Other subjective distress may be related to the interoceptive exposure procedures and administration of the distress tolerance laboratory tasks (breath-holding and mirror tracing persistence task – computerized version [MTPT-C]) including temporary discomfort, such as frustration and other temporary symptoms of psychological stress. Any distress will be minimized by assurances that participant responses are confidential, that they can refuse to answer any particular question they do not want to answer, discontinue any laboratory task, and are free to withdraw from the study at any time without penalty. In addition, referrals will be provided to participants during consent and will be available upon request, in the event that participants are experiencing distress related to the study protocol or otherwise. Any distress will be minimized by assurances that participant responses are confidential, that they can refuse to answer any particular question they do not want to answer, discontinue any laboratory task, and are free to withdraw from the study at any time without penalty. During the course of participation in the research, a participant may have questions about the assessment procedure, interoceptive exposure procedures, or distress tolerance tasks. A project staff member or therapist will be available to answer questions. To prevent discomfort or embarrassment, staff undergoes considerable training in building rapport and skillful interviewing. Research staff members will available to answer questions subjects may have about the assessment. Subjects are informed prior to the assessment that they may choose to skip any question or procedure they find uncomfortable. Discomfort experienced during the distress tolerance tasks is expected to dissipate soon after participants terminate the tasks. The close monitoring of objective and subjective effects by direct observation, interviewing, and self-ratings will allow emergent adverse effects to be detected immediately. If

any individual becomes overly distressed or distraught, the assessment will be stopped immediately and a staff clinician will talk privately with the affected individual(s). In addition, referrals will be provided to participants during consent and will be available upon request, in the event that participants are experiencing distress related to the study protocol or otherwise.

b. **Coercion.** There is a potential for issues related to coercion to participate in this study. Participants may feel that receipt of OAT or their standing in the OAT clinic is dependent on participation in the study. Participants will be reminded throughout the study that participation is voluntary and that the study team will assist the participant in reconnecting with their outpatient BZD provider. Additionally, the study physician will bridge the participant's medication as needed so that there is no gap in treatment.
c. **Breach of confidentiality.** It is possible that data collection could result in breach of confidentiality. For participants in the proposed study, breach of confidentiality in self-report data could reveal that they are engaging in illegal behavior (i.e., breaking laws against possession and use of controlled substances in Massachusetts). However, the risk of breach of confidentiality is also modest, given the safeguards protecting the participants' data.
d. **Overdose.** When the BZD taper begins, participants will begin to be provided a week's worth of BZD medication on a weekly basis until the taper is completed. BZDs when taken in high doses in combination with OAT can cause over sedation and respiratory depression, and can increase the risk of overdose death. The risk of causing overdose by providing a week of BZD medication in those already prescribed BZDs is the same or less than usual, given these participants are already receiving BZDs on a weekly or longer basis. For those not prescribed BZDs, there is an increased risk of overdose if participants take BZDs in greater quantity than we prescribe to them or if they are combining the BZDs we prescribe with other respiratory depressants. But there are risks of not prescribing BZDs to this group; these participants have reported regularly using BZDs obtained illicitly and may already be taking them in overdose or are at risk of BZD withdrawal. We will minimize overdose risk by excluding people with recent illicit opioid use which suggests instability in someone's addiction disorder. We will obtain weekly urine drug and breathalyzer tests to monitor for substance use including respiratory depressants such as illicit opioids and alcohol. We will also be monitoring for over sedation during weekly physician visits which may lead to a temporary hold of BZD medication. And finally, we will be conducting a pill count at the beginning and the end of the study to help determine if participants are taking more medication than prescribed (see Study Intervention).
e. **Benzodiazepine withdrawal.** All participants in this study will undergo gradual discontinuation of BZDs. All participants will be informed of potential risks, including those related to adverse effects from the BZD discontinuation process. Possible adverse effects of BZD taper include: anxiety, insomnia, irritability, nightmares, sensory disturbances, tremor, tinnitus, anorexia, diarrhea, and nausea. If the BZD taper is improperly administered (too rapid), then possible adverse effects include hypertension, fever, delirium, hallucinations, seizures, and death. Participants in prior BZD discontinuation trials very rarely required hospitalization as a direct result of the BZD taper. All participants will receive a medical alert bracelet and emergency card to inform medical providers that they are receiving a BZD taper. Comprehensive screening will exclude participants who would be placed at significant risk, such as prior benzodiazepine withdrawal seizures, as a result of participation in this study.
f. **Medication Adverse Effects**. Some participants will receive SSRIs for anxiety/mood symptoms and/or non-benzodiazepine hypnotics for insomnia, if these symptoms occur during the BZD taper. Side effects of SSRIs may include: nausea, diarrhea, weight gain, dizziness, blurred vision,

dry mouth, headaches, and sexual dysfunction. The hypnotics, used in the proposed study, trazodone and mirtazapine, may also have side effects. For trazodone, side effects may include: dizziness, sweating, blurred vision, and less commonly, confusion, headache, change in heart rate, and shortness of breath. For mirtazapine, side effects may include: decreased or increased movement, confusion, shortness of breath, and rash.

g. **Interoceptive Exposure Risks**: Interoceptive exposure approaches focus on providing patients additional practice in tolerating somatic sensations that trigger benzodiazepine use and will be personalized to each participant. The participant may be asked to hyperventilate, head roll, or jog in place. The participants will be provided with a description of the tasks, sensations the exercises will evoke, and strategies to attend to and tolerate these symptoms. Participants will also be existed to inform research staff of any pre-existing conditions that the tasks may exacerbate, so the research team may personalize the exercise. There are associated risks with these tasks, if the participants has pre-existing physical health concerns (e.g. high blood pressure, heart problems, or joint pain). Hyperventilation may have dizziness, light-headedness, numbness, blurred vision, and hot flashes or sweating. Participants may be asked to jog in place, which will increase heart rate and may cause joint, muscle or ligament strain (depending on the physical shape of the participant). These tasks will be very low impact and for brief time spans, and the study provider will terminate the exercise as needed. If the participant is unable to complete these tasks at all, due to previous health conditions, the study PI may determine they are not the right fit for the study and recommend discontinuation.

6.2 Potential Benefits

Anticipated benefits are as follows: 1) all participants may have lower risk of BZD misuse, overdose death, and OAT treatment failure as a result of discontinuing BZD use, 2) if found to be effective, this treatment could reduce the health risks of BZD use in the population of patients receiving OAT, and 3) the results will be used to advance understanding of the roles of distress tolerance in BZD discontinuation.

6.3 Analysis of Risks in Relation to Benefits

The largest risks to participants are related to the BZD taper, which is happening as part of the participant's clinical care and not for research purposes. If the BZD taper is properly administered, the risk of serious adverse effects is low. Because BZD use has been associated with negative consequences including overdose death in the patients taking OAT, the risks are judged to be acceptable relative to the anticipated benefits.

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:

a) Age 18 or older
b) Receiving OAT (methadone or buprenorphine) for at least 2 weeks

c) Regular BZD use defined by BZD use 3 or more times per week in past month by self-report and positive urine screen at time of recruitment
d) Provides permission to contact current BZD prescriber if being prescribed BZDs
e) Speaks English
f) Wants to discontinue BZD use

7.2 Subject Exclusion Criteria

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

a) Pregnant, confirmed by urine pregnancy test
b) Cognitive impairment, as indicated by Montreal Cognitive Assessment
c) Any past month illicit opioid, barbiturate, cocaine, unprescribed z-drug, unprescribed amphetamine, or synthetic cannabinoid use determined by self-report or urine drug test
d) Receiving ongoing psychosocial treatment for BZD use disorder
e) Uncontrolled seizure disorder (i.e. seizure in prior 90 days), or past BZD withdrawal seizure
f) Current suicidality or homicidality
g) Current psychotic symptoms

8 Study Intervention

<u>Experimental condition</u>

In the study's experimental condition, Distress Tolerance - Benzodiazepine Discontinuation (DT-BD), is a psychosocial intervention paired with a gradual benzodiazepine taper. The aim of the psychosocial intervention is to improve individuals' ability to tolerate distress in order to assist benzodiazepine discontinuation in patients treated with OAT. There will be 5 sessions between therapist and participant prior to the start of the benzodiazepine taper. The taper occurs over 9 weeks and involves weekly meetings with a benzodiazepine prescriber during which a gradual benzodiazepine dose reduction will take place.

The DT-BD intervention combines elements of existing psychosocial interventions. Specifically, interoceptive exposure techniques will be paired with elements of acceptance and commitment therapy (ACT) and relapse prevention (RP). Interoceptive exposure involves inducing symptoms that trigger benzodiazepine use and will be personalized to each participant (eg. Hyperventilation, head rolling, and jogging in place to mimic the dizziness and shortness of breath commonly observed in people who are having a panic attack). The purpose of interoceptive exposure is to decrease the fear of symptoms associated with benzodiazepine withdrawal and potentially the condition for which the participant was using benzodiazepines to treat. ACT teaches people skills in accepting distress in the service of their values rather than resisting or avoiding that distress, which may make distress worse or prolong it. Thus, these ACT-based skills are the ideal partner for interoceptive exposure exercises in that they will assist participants in enduring the distress induced by exposure exercises and ultimately, the symptoms of benzodiazepine withdrawal.

After the baseline visit, in the first 5 sessions prior to the start of the benzodiazepine taper, the therapist will clarify the participant's values, discuss the role of benzodiazepines in the treatment of anxiety

disorders, introduce interoceptive exposure exercises, explore thoughts and feelings about stopping benzodiazepine use, and introduce acceptance as an alternative to distress related to stopping benzodiazepine use. In the final 9 sessions, the therapist will continue to work with the participant on interoceptive exposure exercises and the importance of participant's values, introduce mindfulness, teach relapse prevention skills, and do ACT-based exercises that teach cognitive defusion and willingness.

Session Number	**Goals**	**Themes**
1 (Week -4)	Introduction to intervention and treatment philosophy	1) Introductions
2 (Week -3)	Discuss nature of anxiety and BZDs, discuss risks of BZD use in OAT, discuss problems with BZD discontinuation, discuss BZD taper schedules , clarify participant's values, values used to increase motivation for BZD discontinuation	1) Psychoeducation 2) Values clarification 3) Motivation
3 (Week -2)	Review costs of avoidance of anxiety including BZD use, discuss acceptance as alternative to controlling BZD withdrawal symptoms, introduce mindfulness to assist in observing rather than controlling symptoms, introduce interoceptive exposure with aim of practicing ACT-based skills while experiencing BZD withdrawal-like symptoms	1) Problems with control 2) Acceptance 3) Mindfulness 4) Exposure techniques
4 (Week -1)	Introduce cognitive diffusion, discuss value-driven behavior as alternative to avoidance, further develop ability to observe one's thoughts without judgment, in particular thoughts about anxiety/BZD withdrawal, conduct interoceptive exposure	1) Cognitive diffusion 2) Value-driven behavior 3) Self as context
5 (Week 0) Taper begins	Learn to use mindfulness during BZD withdrawal symptoms as a form of exposure, identify situations that might lead to a greater chance of relapse and developing coping skills if a lapse occurs, conduct interoceptive exposure	1) Mindfulness 2) Relapse Prevention
6 (Week 1)	Introduce concept of willingness, help participant choose to experience anxiety/BZD withdrawal without trying to change that experience, conduct interoceptive exposure	1) Willingness
7 (Week 2)	Introduce concept of committed action, identify goals regarding BZD use, link goals to actions, conduct interoceptive exposure	1) Committed Action
8-10 (Weeks 3-5)	Review previous concepts, extend previous concepts to anxiety in general, dealing with setbacks through mindful acceptance, prepare for end of treatment	1) Review concepts 2) Dealing with setbacks
11-14 (Weeks 6-9)	Monitor progress, address setbacks through mindful acceptance, review coping skills	1) Review concepts 2) Monitor progress

Description of Distress Tolerance – Benzodiazepine Discontinuation content

BZD taper

All participants will undergo BZD discontinuation. For those participants prescribed BZDs, we will obtain permission from those participants to contact the participants' outpatient prescribers. We will inform those prescribers of the participants' intent to discontinue BZD use and we will ask those prescribers not to continue prescribing BZDs during the study.

The following description of the BZD taper protocol is a usual clinical care BZD taper. Patients at Boston Medical Center (BMC) might receive such a taper, though there may be slight differences based on clinician or patient preferences. Other clinicians at BMC have been consulted about this taper who agree that this protocol fits in the range of usual clinical care.

We will check the Massachusetts prescription monitoring program to determine the recent BZD dose. For those participants not prescribed BZDs, we will determine the baseline BZD dose through self-report. Once the starting BZD dose is determined, we will maintain participants on this dose until the start of the BZD taper (likely week 2 and 3 of study). Participants will see a study physician weekly to receive their BZD medication for the week until the taper is completed. BZD discontinuation in this study will consist of a gradual BZD taper in dose over 9 weeks. No RCTs have compared the safety and effectiveness of different BZD taper lengths in outpatient settings though most trials used a gradual taper of 8-10 weeks. Typical BZD tapers in clinical settings can range from 4 to 16 weeks, and sometimes longer (though research suggests that very long tapers of >6 months in OAT patients rarely lead to successful discontinuation[18]). The taper will be flexible in that the study physician will utilize clinical judgement to lengthen the taper if necessary, depending on the severity of the participant's withdrawal symptoms. Anchor points will be set (33% reduction in dose after 2 weeks, 50% mid-treatment, 100% by week 8) to emphasize the time-limited nature of the taper.

Safety monitoring for participants will be supervised by the study physician. Participants may have BZD medication temporarily held if the participant is felt to be over-sedated or tests positive for illicit drugs that are respiratory depressants (typically opioids). We will also conduct pill count at the beginning and the end of the study. If a participant's number of pills is short by >20%, then the study team will meet and discuss the possibility of the participant's discontinuation from the study.

Participants are required to attend all 14 study visits including the baseline assessment. If a participant misses a study visit and research study staff are unable to get in contact with them up until 14 days after their missed appointment, they will be considered discontinued from the study. If a participant decides to discontinue participation during the study before the BZD taper is completed, we will contact their BZD prescriber and provide a bridge BZD prescription until they can be treated by their BZD prescriber.

9 Study Procedures

See the Appendix for the schedule of events.

9.1 Recruitment

Patients will be recruited from Health Care Resource Centers (HCRC) Boston, Faster Paths to Treatment Urgent Care Center at Boston Medical Center (BMC), the Behavioral Health Clinic (BHC) clinic at Boston Medical Center (BMC), and the Office Based Addiction Treatment (OBAT) Program at BMC. HCRC Boston provides OAT treatment for over 650 patients, the BHC clinic for over 150 patients, and the OBAT Program for over 600 patients. We will advertise the study by making an announcement of the study at clinic staff meetings. The research team will work with physicians and clinicians to ensure that they are aware of this research opportunity in order to facilitate their ability to refer potential participants to the study team. Potential participants identified by clinical staff can be given a study flier, which will detail the purpose of the study, eligibility criteria, and research staff contact information. Interested patients will be able to call the phone number or contact the email address for the research team included on these advertisement materials in order to learn more information about the study. In addition, providers may obtain verbal consent from patients to have study staff call to invite them to participate. If the patient provides verbal consent to have research staff contact them, providers will then inform study staff that the patient is interested and expecting a phone call, and will pass along their name and contact information to the research staff. Providers may additionally obtain verbal consent from the patients to have study staff wait outside patients' clinical appointments in one of the above referenced settings to ask if they would be interested in learning more about a research opportunity. If the patient indicates interest, then a member of the research team will bring them to an identified private space in the clinic that does not interfere with their clinical appointment. Any discussion of the study will only occur in a private space. In the private space, they will be provided more details about the research study. If they are interested, potential participants will be asked to complete a brief screening interview using the study screening script that will involve asking questions based on the inclusion and exclusion criteria. If no private space is available, interested participants will be given a study flier with study details and research contact information, and/or collect their contact information and ask permission to contact them at a later time to provide more information about the study and conduct the screening interview over the phone.

Participants who appear to meet study criteria and are interested in participating, will be scheduled for a more comprehensive baseline assessment. At the baseline assessment, before delivering informed consent, research staff will review/confirm eligibility criteria previously done during initial screen. If the participant does not meet eligibly criteria (e.g. recently becoming pregnant), they will be unable to participate in the study and the eligibility data collected at baseline will be destroyed. For those who are eligible and consent, the eligibility criteria checklist will be saved along with their research study documentation. For those who are eligible but do not consent, their eligibility checklist will be destroyed.

IRB approved advertisements/fliers may be posted throughout Boston Medical Center or its network of affiliated behavioral health clinics with permission. IRB approved advertisements may also be placed in newspapers.

9.2 Consent

Candidates will be asked for informed consent before the comprehensive baseline assessment. Informed consent will be conducted in person in a private office in the BMC Department of Psychiatry's Research Center in the Doctor's Office Building or in the Behavioral Health Clinic (BHC) clinic in the Dowling Building at Boston Medical Center (BMC). Participants will then be asked to sign a consent form.

Informed consent will involve providing candidates an IRB-approved copy of the Informed Consent Form to read, or participants will be able to access an electronic version of these forms and can provide an e-signature through drawing their signature on the screen (phone, computer, or tablet/Ipad) with their finger, mouse, surface pen, etc. Appropriately qualified and trained study personnel will explain all aspects of the study in lay language and answer all of the study candidate's questions. Study staff members are trained in Boston University Medical Center (BUMC) IRB policy and will closely follow consent procedures as outlined by the BUMC IRB. Research staff will explain all aspects of the study, including the intervention approach, experimental nature of the research, potential risks and benefits, and the expected duration and time commitment of their participation. Potential participants will be permitted to take an unsigned consent form home with them to think about whether or not they'd like to participate. From the time of explanation of the research study, potential participants will be allotted 7 days to decide whether they would like to participate in the research study. Potential participants will be given study contact information, should they have any questions or concerns, during those 7 days. Candidates who remain interested after receiving an explanation of the study will be delivered the Assessment of Capacity to Participate in Clinical Research to test his/her understanding of the project, the purpose and procedures involved, and the voluntary nature of his/her participation. Those who cannot successfully answer the items on the Capacity Questionnaire will have the study re-explained by research staff with a focus on aspects they did not understand. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the Informed Consent Form. Participants will be given, mailed, emailed (depending on preference) a copy of their signed consent form. No baseline assessments will begin until after a signed research consent form is obtained.

9.3 Baseline Assessment

See schedule of events for breakdown of assessments and study timeline

Baseline Assessment:

After informed consent is obtained, participants will begin their baseline assessments. The baseline assessments will be delivered in person, either at our research office or at a BMC clinical space.

First, participants will be delivered a urine drug test and pregnancy test, and the 30-day Timeline Followback (TLFB), which will be used to measure drug use in the past 30 days. Participants will not be eligible to continue with the study a) if their urine drug screen shows use of illicit drugs (including opioids, cocaine, barbiturates, unprescribed z-drugs, unprescribed amphetamines, or synthetic cannabinoids), b) if they report use of illicit drugs (including opioids, cocaine, barbiturates, unprescribed amphetamines, unprescribed z-drugs, or synthetic cannabinoids) in the past month, or c) if their urine drug screen shows that they are currently pregnant. The urine pregnancy screen results will be available immediately during their visit. However, the urine drug screen results may take up to several days to process.

- If the urine screen shows that the participant is currently pregnant, the participant will not be eligible to continue with the study and baseline assessments. These participants can return after 30 days, if they choose, where they will be asked to re-screen with the urine drug test, pregnancy test, and the TFLB. If at that second visit, their pregnancy test is negative and they

report no illicit drug use in the past 30 days, they will be able to take the baseline assessments. Pending the results of their urine drug screen, they will be able to continue with their follow up study visits.

- If the participant is not currently pregnant, but reports use of illicit drugs (including opioids, cocaine, barbiturates, unprescribed amphetamines, unprescribed z-drugs, or synthetic cannabinoids) in the past month on the TLFB, the participant will not be eligible to continue with the study and baseline assessments. These participants will have the opportunity to return in 30 days where they will re-take the urine drug test, pregnancy test, and the TLFB. If at the re-screen, they are not pregnant and report no use of illicit drugs in the past month, they will be able to take the baseline assessments. Pending the results of their urine drug screen, they will be able to continue with their follow up study visits.
- The urine drug screen results may take up to several days to process. If the pregnancy screen shows the participant is not currently pregnant, and the participant reports no use of illicit drugs in the past 30 days, the participant may complete the baseline assessments and receive the $30 payment. When research staff receive the results for the urine drug screen and it shows use of illicit drugs (including opioids, cocaine, barbiturates, unprescribed z-drugs, unprescribed amphetamines, or synthetic cannabinoids), they will not be eligible to continue with the study. However, if they would still like to participate in the study, they will have the opportunity to return in 30 days where they will re-take the urine drug screen, pregnancy test, and TLFB. If at the second screen, they are not currently pregnant, report no illicit drug use in the past 30 days, and there is no presence of illicit drugs from their urine screen, they will be enrolled in the study.

For those who are not eligible to be in the study and/or choose not to return after 30 days for a re-screen, we can provide referrals and contact information for alternative services at Boston Medical Center for urgent care and benzodiazepine use, including the Outpatient Behavioral Health Clinic at BMC and Faster Paths to Treatment Center at BMC. These programs are listed in the consent form under the Treatment Alternatives Section.

Those who are eligible to continue with the study will be asked to complete baseline assessments. These could be completed at our research office or in the clinic through REDCap survey links, whichever is most convenient and appropriate for the patient. Participants who complete the surveys online will be sent REDCap survey links to their emails or mobile phone. A trained research assistant (RA) will collect demographic information and administer the Mini-International Neuropsychiatric Interview (MINI)[30], a brief, 15-minute psychiatric diagnostic interview. Motivation for BZD use, alcohol and other drug use by self-report, BZD withdrawal symptoms, distress tolerance measures, affect and sleep symptoms, and suicidal ideation will also be assessed during the baseline assessment. Participants who complete the baseline assessments will receive a $30 payment in the form of a BMC Clincard for their time and participation.

Daily assessment: In addition to the assessments listed in the table above, we will measure substance use, BZD medication adherence, and sleep duration and quality on a daily basis. Each participant will be sent a daily REDCap survey link either to their mobile phone number or email, and asked to complete a brief questionnaire for the previous day. Participants will be sent the survey link through REDCap to their email address or, if preferred, to their mobile phone number using Twilio, a third party service,

that enables SMS text survey link distribution to phone numbers through REDCap. If they do not own a mobile phone, we will provide a phone free of charge for use during the study. After the completion of the study or study drop out, participants will be asked to return the phone.

After informed consent is obtained and baseline assessments are completed, participants will begin with their first session of the intervention.

9.4 Assessment Tools

BZD and Other Drug Use. We will measure benzodiazapine history using the BZD history questionnaire[32,33]. At baseline and weekly through the taper, we will measure alcohol, BZD, OAT, and illicit drug use with urine screening and self-report. The 30-day Timeline Followback (TLFB)[34] will be used to measure self-report of drug use at baseline. We will send a REDCap survey link to the participants' mobile phone number or email to measure substance use during the week. Urine BZD tests will include immunoassay for all BZDs and liquid chromatography–mass spectrometry for lorazepam and clonazepam, as these BZDs have a high false negative rate on immunoassay tests[35,36]. A breathalyzer test will be performed at each visit. We will assess for BZD withdrawal symptoms using the Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B)[37].

BZD Medication Adherence. We will send a daily REDCap survey link to the participant's email or mobile phone to assess daily BZD medication adherence.

Affect and Sleep. At each visit, anxiety symptoms will be assessed using the Overall Anxiety Severity and Impairment Scale (OASIS)[38] and the Patient Health Questionnaire (PHQ-9)[39] will be used to assess depression symptoms. Sleep quality will be assessed using the Pittsburgh Sleep Quality Index (PSQI)[40] at baseline and on a weekly basis. Additionally, sleep duration and sleep quality will be measured on a daily basis using a REDCap survey link.

Distress Tolerance. Self-reported DT measures will include the Distress Intolerance Index[41], the Acceptance and Action Questionnaire-II[42] and the Anxiety Sensitivity Index[43]. Behavioral DT measures will include breath holding and the computerized Mirror Tracing Persistence Task (MTPT-C)[44].

Suicidal Ideation: At the baseline assessment, we will measure suicide risk, severity and immediacy of risk, and level of support needed using the Columbia-Suicide Severity Rating Scale (C-SSRS).

Feasibility and Acceptability. We will measure recruitment and retention rates, number of visits attended, and participant feedback of intervention during an in-depth qualitative exit interview.

In this study, data will be collected from participants who are or may present to assessment and intervention appointments intoxicated. Upon arrival to intervention and assessment appointments, all participants will receive a Breathalyzer test prior to assessment interviews; if a participant appears intoxicated or impaired, the RA will reschedule the interview. If participants experience anxiety and insomnia during the BZD taper, we will offer an SSRI or a dose increase if already prescribed for anxiety, and non-BZD hypnotics (e.g. trazodone or mirtazapine) for insomnia.

9.5 Exit Interview

Exit interview – At the end of the taper, participants will undergo an in-depth qualitative exit interview. Interviews will be audio recorded, and written notes containing no individual participant identifiers will be taken by the RA. Participants will be asked to provide extensive feedback during exit interviews to assess what was/was not helpful, what would have been helpful, and any feedback on intervention content, method of delivery, or structure.

Participants will receive $30 at baseline visit and will be paid $2 for each daily mobile assessment from week 2 to week 13 (earning up to $168). They will additionally receive a $50 ClinCard for a post-intervention interview. Participants can earn up to $248 for participating in the study.

Safety Assessment

If the study staff learns of any acute safety concerns, such as current thoughts about suicide, self-harm, or intent to harm others, abuse, neglect, or other reportable conditions, research study staff will interrupt study activities and utilize the Standard Operating Procedure for Safety Assessments Endorsement of Suicidality, Risk to Self or Others (SSOP) Safety Assessment Form. If the participants brings up thoughts of suicide or self-harm, research staff will utilize the Columbia-Suicide Severity Rating Scale (C-SSRS) to assess participant risk. If the participant brings up intent or harm others, abuse, neglect or other reportable conditions, research staff will complete the Acute Safety Assessment to probe frequency and severity of the concern to identify participants who may be at immediate risk and require further intervention. Upon completion of the C-SSRS and/or Acute Safety Assessment, research staff will contact the study PI who will conduct an acute safety assessment over the phone or in person. PI will then utilize clinical judgement to determine further course of action.

Removal of Participants

All instances of study drop out will be documented, including reason for dropout, who decided the participant would drop out (participant, study staff or PI), and whether the drop out resulted from burden of intervention, study assessment, or another reason. Withdrawn participants will be encouraged to participate in the exit interview to provide feedback on why the intervention did not work for them and suggestions for improvement. Participants may withdraw voluntarily at any time for any reason. If the participants withdraw from the study or the intervention, they will be asked to return the mobile phones.

There are two types of participant withdrawal: “intervention withdrawal” and “study withdrawal”.

1. **Intervention withdrawal:** A participant drops out of the treatment (either because they are no longer interested or because the study PI feels the intervention is no longer appropriate), but still provides the research team with post-intervention data by completing assessments and exit interview.
2. **Study withdrawal:** A participant (or provider on behalf of participant) explicitly communicates that they are no longer interested in being a part of the study at all, including future assessments and compensation. Cases of intervention withdrawal are not automatically considered to be study withdrawal unless the participant specifically states that they never wish to be contacted again by the study, or if the study investigator deems any future contact would be inappropriate.

Participants may be removed if:

- If the results of their urine drug screen tests positive for illicit drugs.
- If the number of benzodiazepine medication during the pill count is short of the expected amount by over 20% at both visits.
- If the participant tests positive for cocaine, synthetic cannabinoids, non-prescribed opioids, barbiturates, z-drugs (for example, Ambien), or amphetamines during the urine drug screen or they report using these substances a total of 3 times during the study.
- If there is evidence of ongoing substance use of illicit substances, they may be removed and referred to a higher level of treatment including inpatient detoxification or residential treatment.
- If the participant becomes pregnant over the course of the study.
- If the study investigator or treating provider feels the study is negatively impacting the participant's health or wellbeing resulting in increasing severity of illness that is clinically assessed as such by the study PI. Such cases will be assessed clinically and study PI will determine whether the participant should be removed from the study.
- If the participant becomes suicidal and presents with clinically determined safety risk to self or others.

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

10.1 Definitions

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, 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.

10.2 Safety Review

Both the risks listed in Section 4.1 and unknown risks will be monitored as follows:

The study PI, Tae Woo Park, will review and update this protocol and all procedures as needed and will provide oversight. Monitoring will be done by the PI in consultation with mentors, the IRB and NIDA, the study sponsor.

What is Monitored. All procedures will be monitored to ensure that they conform to the approved protocol. In addition, monitoring will be done of all unforeseen circumstances that might arise and affect safety; of all reports of serious adverse events as defined above; of other significant adverse events (adverse events that lead to drop out by the participant or termination by the investigator); and of unexpected adverse events resulting from the study.

Frequency of Monitoring. Monitoring of adherence to the study protocol and emergent unanticipated adverse events will be conducted by the PI on an ongoing basis. This monitoring will be discussed with mentors during regularly scheduled meetings. Participants will be given contact information so that they can inform study staff of events that occur in between study visits. In addition, monitoring by the IRB is conducted at the annual continuing reviews as scheduled by the IRB and upon receiving reports of adverse events from the PI.

Oversight. The PI is responsible for the general oversight for all research activities. Each intervention project will have a yearly review of its DSMP during the regular continuing review process, outlining the following points: (a) reassessment of the risks and benefits to study participants, (b) participant recruitment, accrual, and retention, (c) data quality and confidentiality, (d) consideration of external scientific or therapeutic developments with impact on the safety of participants or the ethics of the

study, (e) review any adverse events. The PI will update the general DSMP procedures as needed. All modifications to the protocol or DSMP will be communicated to NIDA, the study sponsor.

10.3 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 involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- 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 no recommended changes will be reported to the IRB at the time of continuing review.

10.4 Stopping Rules

The study has no pre-defined stopping rules. Should a fatal or life-threatening overdose/withdrawal event occur, the PI will revise or withhold the research plan and discuss with mentors, the IRB, and NIDA.

11 Data Handling and Record Keeping

11.1 Confidentiality

Coded data: A unique ID will be used to identify individual records, and all data and samples will be labeled only with this study ID number (i.e., not the participant's name, date of birth, medical record number, etc). The unique study ID will be linked to participant identifiers via a mastercode/key. Restricted access to participant contacts information and the mastercode/key will be limited to members of the research staff as necessary to complete their duties. Locator/contact information and a master enrollment list will include identifiers, but participant names will not be entered into the analytical database. The mastercode/key that links study data to identifiers will be stored separately from the study data (i.e., in separate physical files and separate databases) and protected as described below.

Data Management and Security to Protect Privacy: The research study team will assure high quality forms, monitor data quality, and track and link the multiple data sources. Data will be linked and entered using multiple checks. The research study team will manage data collection forms, design the database management system for data entered and for participant tracking, implement procedures for quality control, and provide statistical programming.

All data for study purposes will be collected with Apple iPad tablets or electronic survey links using the Boston University Medical Campus' installation of REDCap data collection system, a software tool developed at Vanderbilt University and made available through the Clinical and Translational Science Awards network (CTSAs). To help protect and secure the data stored in REDCap's database, the software application employs several methods to protect against malicious users who may attempt to identify and exploit any security vulnerabilities in the system. Access to the REDCap data entry website will be based on permissions granted by username and password which will be managed by the Boston University Clinical and Translational Sciences Institute for the Medical Campus Office of Information Technology (OIT). Only authorized study members will be able to enter or view data. The login information (username) of the person submitting the information, the date and time submitted, and other navigational information will be automatically obtained and stored in the database.

Boston University's installation of REDCap is HIPAA compliant. Information posted on forms will be electronically encrypted using secure socket layering (SSL) encryption technology so that only the intended recipient can decode the data. Data will reside on a secure, password protected server at Boston University Medical Center (BUMC) to which only designated individuals have access, thus providing a secure environment for all project data. The database will be automatically backed up on a nightly basis. Files stored on BUMC servers will be protected by electronic 'firewalls' that restrict access to designated users. Restrictions and permissions to update the database will be controlled through the REDCap web application.

Because the server will be part of the BUMC network NT domain, only connections from users authenticated from the domain controller are accepted, thus providing a secure environment for all Center data. Specifically, the policy for computer systems security implemented at BUMC:

- Provide physical security of data. All central systems are physically secured behind locked doors with access restricted to key personnel in the OIT. Access through the primary door is also protected by an alarm system that is tied directly into the on-site central emergency response security control center. Written policies exist for contingencies to provide access to the room to those not explicitly authorized.
- Provide virtual security via connectivity. Internal access to all systems is done via Microsoft Challenge Handshake Authentication Protocol. With the exception of internet provider-based services, external client access must first gain access to the internal network before connecting to the systems. This connection is initiated via a Virtual Private Network connection using Point-to-Point Tunneling Protocol or through the University's modem pool which require Kerberos authentication.

All data are protected with disaster recovery via several methods:

- Hardware redundancy: Several stages of redundancy exist at the hardware level to minimize failure: dual-redundant power supplies exist on each disk array; hot-spare disk is configured to automatically self-heal in the event of a disk failure in the array; emergency power generators

ensure a 100% electrical uptime; and uninterrupted power supplies present the systems with conditioned steady-state power.

- Data backup: The data are backed up on a regular schedule. All tapes are moved off-site on a daily basis and are stored in a fire-proof safe. Cycle-time of backups is approximately two months with the exception of a yearly archive which is retained for a one-year period.
- Data Security: All data are stored on NT File Systems with password-protected files and directories.

The BUMC REDCap Server has implemented a mix of preventive and detective security measures:

- Two factor authentication required for both admin and user access
- Require a password change every quarter for users
- Server is placed behind data center firewall
- Requires two-factor authentication and only permits for specific admin(s) that need to access the server
- Inform PIs that they need to remove investigators who are no longer involved, and periodically (ideally quarterly) review accounts
- Server is protected by intrusion prevention measures (firewalls/snort)
- Server is part of change management and vulnerability management programs to ensure server is patched within 30 days of vulnerability notification

Electronic survey links will be sent to participant's emails or phone numbers using REDCap and REDCap enabled feature, Twilio. Twilio is a third-party web service that provides the functionality for researchers to send REDCap survey invitations via SMS text messaging. Twilio will have access to the participant's phone number. When a BU REDCap admin enables Twilio for a REDCap project, BU REDCap verifies that the Twilio Request Inspector has been disabled. This setting ensures that survey participants' phone numbers do not get permanently logged on Twilio's servers, but instead remain securely in the BU encrypted REDCap server. Twilio will not have access to participant PHI data.

The qualitative interviewers will be audiotaped, with subjects' permission, using a digital voice recorder or audio recording program on our BMC encrypted study laptops. Each digital audio file will be coded with subject unique identifiers, only connected to identifiers (PHI) via a separate, password-protected, master code. These files will be stored on a password-protected, encrypted BMC network. The coded audio file will additionally be sent to a commercial service for transcription.

All paper records (i.e. signed consent forms) will be stored in locked storage spaces (cabinets or drawers) in a secure research office. Only study staff will have access to the key to get into these storage spaces. Participant forms will be stored in a single folder that is labeled with their respective study ID number.

11.2 Source Documents

Study records will include consent forms, transcriptions of participant exit interviews, and participant interviews that will be audio recorded on a digital voice recorder. The audio recordings will be transcribed by a commercial transcription service. These transcriptions will be the primary source documents for this study. The interviewer, the PI or a trained research assistant, may also take notes on the qualitative interview guide during the interview and these notes may also serve as source documents for study data. Additional participant data will consist of a brief, 15-minute psychiatric diagnostic interview, measurement of motivation for BZD use, a urine drug test, alcohol and other drug use by self-report, BZD medication adherence by self-report, BZD withdrawal symptoms, distress tolerance measures, and affect and sleep symptoms. REDCap, described more generally below, will be used to assess BZD medication adherence, substance use, and sleep (sleep duration and sleep quality). We will ask participants to provide once daily reports via REDCap survey link sent to participant's email or mobile phone. If participants do not own a phone, we will provide them with a phone with one.

This study will utilize REDCap (Research Electronic Data Capture), a software toolset and workflow methodology for electronic collection and management of clinical and research data, to collect and store assessment data. The Boston University School of Medicine Research Department will be used as a central location for data processing and management. REDCap provides a secure, web-based application that provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, real-time data monitoring/querying of participant records, and variations of data exporting/importing.

11.3 Case Report Forms

This study will not utilize case report forms.

11.4 Study Records Retention

The transcriptions and notes from the interviews, as well as assessment data, will be retained for at least seven years after the completion of the study and will be destroyed after the publication of the final journal article that uses this data. The audio files will be destroyed after they have all been transcribed.

12 Statistical Plan

12.1 Study Hypotheses

DT-BD intervention will be found to be acceptable and feasible treatment arm for OAT patients discontinuing BZDs.

12.2 Sample Size Determination

This is a small pilot study to assess the acceptability and feasibility of the DT-BD intervention. A total of four participants will be recruited. If there is early dropout from the study, we will replace participants until we have an adequate rate of completion that allows for evaluation of all of the DT-BD intervention

modules. Interviews from this pilot study will be used to further refine our interventions in preparation for a larger, randomized pilot trial testing DT-BD vs. a control condition in this patient population.

12.3 Statistical Methods

The primary outcome for this study is the acceptability and feasibility of the intervention. The primary outcome data will consist of transcribed, in-depth interviews after the completion of the BZD taper. A qualitative research approach will be used to analyze this data. The analysis plan is centered on several domains, and within each of the domains, the investigator will draw comparisons, looking for overlap and differences, themes and trends. In addition, the investigator will continually look for newly emerging topics and patterns. Though we are collecting quantitative data including substance use, affect, sleep, and distress tolerance, we are only doing this for acceptability and feasibility purposes. This is in preparation for a future, larger trial during which we will be using these proposed measures for quantitative analysis.

13 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 Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, 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.

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.

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15 Appendix

Schedule of Events

	Visit 1: Baseline Assessment	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6***	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14 Taper Ends**
Consent	**X**													
Informed Consent	**X**													
Demographic Questionnaire	**X**													
MINI	**X**													
BZD History Questionnaire	**X**													
Urine BZD Test	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Timeline Follow-back (TLFB)	**X**													
Clinical Institute Withdrawal Assessment-Benzodiazepines (CIWA-B)	**X**					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Distress Intolerance Index DII	**X**				**X**									**X**
Acceptance and Action Questionnaire-II (AAQ-II)	**X**				**X**									**X**
Anxiety Sensitivity Index	**X**				**X**									**X**
Breath holding and Mirror Tracing Persistence Task (MTPT-C) results	**X**				**X**									**X**
Overall Anxiety Severity and Impairment Scale (OASIS)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Patient health Questionnaire (PHQ-9)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Pittsburgh Sleep Quality Index (PSQI)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Columbia-suicide severity rating scale (c-ssrs)	**X**													
Acceptability – Attendance, treatment retention, participant feedback	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

In depth qualitative exit interview														**X**

* First visit after start of taper