Reducing cannabis use for sleep among adults using cannabis

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BACKGROUND

Both the number of users of medical cannabis and the number of states legalizing cannabis for medical and recreational purposes are rapidly on the rise.[1,2] Research on medical cannabis patients indicates that they are primarily lower-income, middle-aged adults, with poor mental health and physical functioning, who use cannabis heavily. Recent national survey data, for example, indicate that adults who use medical cannabis are *more than four times* more likely to use cannabis daily compared to only recreational users[3] – *a pattern of use linked to sustained intoxication and significant impairment in cognitive and social functioning*.[4-9] Innovative strategies to improve the health and functioning of this population are critically needed. Our data from 800 patients seeking medical cannabis indicate that insomnia is a chief comorbidity among medical cannabis users and a principal reason for cannabis use, with 80% reporting regularly using cannabis for insomnia.[10] We hypothesize that addressing insomnia in these individuals with evidence-based strategies will lead to improvements in sleep and health-related functioning.

Cognitive behavioral therapy for insomnia (CBTi) is an evidence-based treatment targeting behavioral and cognitive factors critical to chronic insomnia. Multiple controlled trials indicate that 70-80% of patients with chronic insomnia (alone or accompanied by other health conditions) benefit from CBT,[11-13] as many as 50% achieve remission from insomnia,[14,15] and treatment benefits are sustained over time.[16-19] However, previous studies have excluded regular cannabis users; consequently, the benefits of CBTi for improving insomnia, functioning, and reducing reliance on cannabis have not been evaluated in these individuals. Our group has shown that CBTi improves sleep and functioning in patients with alcohol use disorders (AUD), and that CBTi can be successfully administered by telephone to non-AUD patients with chronic insomnia. Telehealth delivery is a key modality to expand access to CBTi in the general population and it is likely to have a particularly high impact for individuals who are disconnected from standard healthcare settings, such as adults with medical cannabis certification. However, adaptation and iterative refinement of this promising treatment via telephone delivery is necessary to improve the relevance to non-treatment-seeking individuals who use cannabis for insomnia.

The overall premise for this study is based on a combination of observational and correlational work that highlights the high prevalence and robust associations between cannabis use and sleep disturbances combined with randomized trials that demonstrate the existing efficacy of CBTi in different patient populations. The overarching goal of this proposal is to modify and refine this evidence-based treatment to increase relevance for individuals using cannabis for insomnia, to assess the distribution and variability of the primary variables of interest, and to measure potential mechanisms of change. These aims would provide all of the elements required for a future fully-powered randomized trial of the longer-term efficacy of CBTi-CB among those using cannabis. This line of research would be the first to evaluate a highly effective sleep-focused intervention and determine the effects on sleep-related and non-sleep-related cannabis use in a non-treatment seeking population.

OBJECTIVES

The objectives of this project are to adapt and tailor an existing intervention (CBTi) for adults who use cannabis to be delivered remotely via video chat or telephone therapy sessions, and to evaluate the acceptability and feasibility of this intervention. This study will include (1) tailoring the existing CBTi intervention to the population based on qualitative data collected from 10 individuals who use cannabis for insomnia, and (2) beta testing the revised CBTi intervention and a developed control condition (Sleep Education Control; SE) in up to 8 individuals who regularly use cannabis for insomnia. Information regarding the feasibility and acceptability of the intervention and study procedures (e.g. wearing a sleep device and completing daily assessments) collected during the beta testing phase will be used to inform the procedures utilized during a subsequent pilot randomized (RCT) controlled trial of CBTi-CB vs. SE. For the pilot trial, 60 individuals who report using

cannabis for insomnia will be recruited from medical cannabis clinics and dispensaries to participate in a pilot randomized controlled trial (RCT) of CBTi-CB versus a Sleep Education Control (SE). Our *central hypothesis* for the pilot RCT is that an evidence-based CBTi approach will improve insomnia and health-related functioning among those who use cannabis to help with insomnia.

The specific aims of the study are:

Specific Aim 1: Adapt and iteratively refine an existing CBTi intervention to (1) address the unique needs of individuals using cannabis for insomnia, and (2) allow the intervention to be delivered remotely via video chat or telephone.). We will also adapt and refine an attention matched Sleep Education Control (SE) condition to be delivered remotely. This aim will be accomplished in two phases. **Phase 1** will include modifying treatment manuals and conducting qualitative interviews with 10 individuals who use cannabis for insomnia to better understand perceptions of the relationships among insomnia, coping, functioning and cannabis use, as well as what might influence intervention adherence. In **Phase 2**, both manuals will be beta-tested with up to 8 participants (4 for CBTi-CB and 4 for SE).

Specific Aim 2: Conduct a pilot RCT comparing CBTi-CB (n=30) to SE (n=30) delivered remotely to (a) assess the acceptability and feasibility of RCT procedures; (b) determine the distribution and variability of the primary outcomes (insomnia severity, health-related functioning); and (c) assess potential mechanisms of change (sleep-related behaviors; sleep-related beliefs; sleep self-efficacy; and cannabis use motivation) within the CBTi-CB and SE conditions.

The proposed project addresses a key objective articulated in the most recent **NIDA Strategic Plan**, specifically, to “develop and test novel treatments based on the science of addiction” (Objective 3.1). This work is significant because of the large and growing number of US adults who use cannabis to manage their insomnia. Given the extent of daily cannabis use in users of cannabis for insomnia, intervening on sleep in this group represents the opportunity to engage and improve outcomes in those with heavy cannabis use. The study is innovative because it targets insomnia, a highly comorbid condition in a group of non-treatment seeking individuals, and proposes that improvement in sleep will reduce cannabis use and improve health-related functioning. The impact is enhanced by leveraging telemedicine approaches to optimize reach of the treatment.

RESEARCH DESIGN AND METHODS

Overview of approach. The purpose of this project is to adapt, iteratively refine, and pilot test an existing CBTi intervention for use in adults who currently use cannabis for insomnia (CBTi-CB). The proposed work is consistent with Stages IA/IB of the NIH Stage Model of Intervention Development.[20,21] Also in line with these recommendations, the pilot trial will gather data on the extent to which participation in the CBTi-CB intervention is associated with changes in the proposed mechanisms of action of the intervention.[20,21] The proposed project has two primary aims: (1) adapt and iteratively refine remotely-delivered CBTi-CB to address the unique needs of individuals using cannabis for insomnia and develop and refine a matched remotely-delivered Sleep Education Control (SE) condition; and (2) conduct a pilot randomized controlled trial (RCT) comparing remotely-delivered CBTi-CB to SE to (a) assess the feasibility of RCT procedures; (b) determine the distribution and variability of the primary outcomes (insomnia severity, health-related functioning); and (c) assess potential mechanisms of change.

Overview setting and existing content of CBT for insomnia and SE conditions.

Study site description. Recruitment for all phases of the proposed study will occur from clinics operated by Michigan Holistic Health and Michigan Medical Marijuana Certification Center (two of the largest organizations

of medical cannabis clinics in the state of Michigan) or from Michigan licensed marijuana dispensaries. We have recruited in both medical clinics for our prior NIDA-funded study and it has been our experience that clinic staff were very supportive and patients were interested in participating in research. Recruitment for the beta testing and RCT phases of the study will occur from cannabis provisioning centers (also called dispensaries) operated by OM of Medicine and Bloom City Club (see letters of support). Dispensaries are generally open from 10am to 8pm on weekdays and see approximately 20-70 patients per day. All dispensaries have designated waiting rooms in which potentially eligible participants can be approached. All recruitment sites understand the nature of our research project and are supportive of us basing our screening and recruitment efforts within their dispensaries.

Structure of CBTi-CB and SE conditions. In order to keep non-specific factors consistent across conditions, CBTi-CB and SE will be delivered in a similar format and over the same time interval. Both conditions will follow a manual and will be delivered by a masters-level therapist. Both conditions will involve six 45-60-minute individual remote therapy sessions - that will be delivered weekly for 6-8 weeks (with a range to be flexible to accommodate participant schedules). Patient modules will be developed for both interventions. We opted to deliver the intervention over the phone or via video chat to maximize engagement and reach, given our prior work indicating that cannabis users are geographically dispersed, responsive to study contacts over the phone, and many face barriers to in-person sessions.

Content and format of CBTi-CB and SE conditions. The CBTi-CB intervention will be derived from CBTi manuals previously developed by our team for a study of individuals with chronic insomnia, which was telephone delivered, and a prior NIAAA-funded study of CBTi in subjects with AUD delivered face-to-face. The content will be revised to focus on cannabis use and sleep and patient materials will be altered to allow remote delivery. The overall structure and sleep-oriented content will remain essentially unchanged. The SE intervention will be developed using modified versions of matched control conditions from two studies of CBT for pain (one funded by VA HSR&D and one funded by NIDA), CBT for suicide risk (a prior NIDA R21 and an ongoing DoD study), and a NINR-funded study of CBTi in post-menopausal women. Aim 1 is devoted to modifying and iteratively refining the content of these conditions.

CBTi-CB. Each CBTi-CB therapy session will follow a format standard to CBTi,[73] which begins by qualitatively reviewing the previous week of sleep/wake diaries and quantitatively summarizing key sleep parameters, which are shared with participants. No single session will be focused exclusively on cannabis use. Instead, content related to cannabis will be integrated into each session's specific insomnia-related focus. Cannabis use is primarily conceptualized as a maladaptive coping response and the treatment will address cannabis use by increasing the use of more appropriate coping strategies and improving self-efficacy to manage insomnia and next-day consequences without cannabis. The current content of the CBTi protocol includes: (1) Sleep Scheduling Strategies: The primary goal of these strategies is to consolidate sleep using behavioral strategies that increase the drive for sleep and stabilize the circadian timing system. Specifically, *sleep restriction* curtails the amount of time spent in bed each night to the patient's estimated average total sleep time to increase sleep drive, thereby enhancing sleep onset and maintenance.[53] Time in bed is gradually increased in subsequent treatment sessions to improve nighttime sleep quality and optimize daytime functioning. *Stimulus control* is designed to associate temporal (bedtime) and environmental (bed, bedroom) cues with rapid sleep onset and to establish a regular sleep-wake schedule;[73] (2) Sleep Hygiene: Sleep Hygiene refers to behaviors, substances, and environmental conditions that can help or hinder sleep. The following sleep-positive practices are promoted: regular meals, pre-bedtime routine, regular exercise, limited intake of caffeine, alcohol, nicotine, and liquids in the evening, and a good quality sleep environment (quiet, dark, and comfortable); (3) Cognitive Therapy: Cognitive therapy in CBTi aims to identify and alter dysfunctional beliefs about sleep and functioning that contribute to maintaining insomnia. Patients are first educated about common insomnia-related cognitive themes (e.g., perceived consequences of insomnia) and

identify individualized sleep-disrupting cognitions and are then taught cognitive strategies to challenge the validity of these unhelpful cognitions; (4) Counter-Arousal Strategies: A common characteristic of insomnia is a predisposition to ruminative thoughts and increased body tension that interferes with the ability to fall or return to sleep.[74] This "hyperaroused" state is often present throughout the day and night in patients with insomnia and is thought to reflect both trait and state components.[75] Brain imaging studies support subjective complaints by patients with insomnia, showing elevated brain activity compared to patients without insomnia.[76] The goals of counter-arousal techniques are to directly address cognitive or somatic hyperarousal through the use of behavioral and cognitive techniques, such as deep breathing/relaxation and constructive worry; (5) Relapse Prevention for Insomnia: Participants review treatment gains and the individualized behavioral and cognitive strategies that were most helpful. Relapse prevention involves identifying high-risk situations for insomnia, promoting realistic appraisals about future insomnia episodes, and identifying behavioral and cognitive strategies for dealing with the inevitable occasional poor night of sleep.[73]

In order to assess for receipt of CBTi-CB content, participants will complete weekly pre-session and post-session assessments related to the content of each session (treatment comprehension measures).

Sleep Education (SE). In order to enhance the scientific rigor and minimize bias, the SE condition will be matched to the CBTi-CB condition in terms of level of attention and the non-specific aspects of receiving social support from a study therapist, without providing individualized recommendations. Proposed content for the remotely -delivered SE control will include: (1) Insomnia History: This session will be devoted to learning about the participant's insomnia history, including triggers that initiated the sleep problem, its duration, severity, and frequency, premorbid sleep characteristics, and previous sleep medication and non-medication treatments; (2) Sleep Education: This session will provide basic education about why we sleep, sleep stages, how sleep is regulated at night, and sleep changes across the lifespan; (3) Substance Use and Sleep: This session will focus on the effects of cannabis and other licit and illicit substances on sleep; (4) Environmental Factors and Sleep: This session will focus on the general factors that contribute to a sleep-conducive environment; (5) Lifestyle Factors affecting Sleep: This session will address the effects of diet, exercise, and napping on sleep. Subjects will also be educated about the importance of regularity of activity and meal times to enhance sleep quality; (6) Sleep Maintenance Strategies: The final session will focus on reviewing treatment gains from the participant's perspective and emphasizing the principles covered over the previous sessions in order to maintain sleep improvements.

Similar to the CBTi-CB condition, SE participants will complete weekly pre-session and post-session treatment comprehension assessments.

Specific Aim 1: Adapting and iteratively refining the CBTi-CB and SE conditions. As noted above, the initial content of the CBTi-CB and SE exists from previously developed treatment manuals; however, the content will need to be modified to fit within a new setting, to be delivered remotely, and to address issues specific to adults who use cannabis. Iterative refinement of the content will occur in 2 phases.

Specific Aim 1 - Phase 1 (Qualitative Interviews). The PIs will draft initial detailed treatment manuals and companion patient modules for CBTi-CB and SE. Each of the existing sessions will be re-written to fit with delivery over the phone and to emphasize content specific to cannabis. The prior manuals included minimal information on cannabis (substance related information focused on alcohol and substances of abuse in general). These will be re-written to focus more directly on cannabis and the ambivalence that participants may feel about changing cannabis use patterns.

The other project investigators (Drs. Bohnert and Conroy) will review the initial treatment manuals and patient modules for comment and, together with the PIs, will constitute an **Internal Advisory Group.** The other investigators bring different areas of expertise to contribute to the treatment manuals and patient modules. For

example, Dr. Bohnert will utilize his expertise in cannabis and factors underlying cannabis use to enhance sections related to harm reduction. Dr. Conroy will draw on her specific expertise in sleep and cannabis to focus on clear communication of the content related to sleep and cannabis. Based on the feedback of the Internal Advisory Group, the PIs will draft a revised version of the treatment protocol.

The project staff will conduct 10 qualitative interviews with individuals recruited from the study sites with subjects who use cannabis for insomnia (men: n=5; women: n=5) to better understand perceptions of the relationships among insomnia, coping, functioning and cannabis use, as well as what might influence adherence to a 6-session remotely delivered intervention. Screening and recruitment for these qualitative interviews will be based in the study sites described above and will mirror the methods used in the prior NIDA cohort study as well as the planned methods for the beta testing in Phase 2 (see below) and the pilot RCT to be conducted for Aim 2.

Potential participants will be approached by study staff in the waiting room at the clinic sites and invited to participate in the study. Study staff will follow the recruitment script which includes eligibility screening questions. No identifying information will be collected from those who are not eligible or choose not to participate in the study. Written informed consent will be obtained from all participants. Participants will receive $50 for the completing the qualitative interviews.

These qualitative interviews will allow for feedback on the potential content of initial drafts of the CBTi-CB and SE manuals. The study PIs will make revisions to the manuals based on this input and these new manuals will be further refined with feedback from the Internal Advisory Group.

Data Analysis. Qualitative interviews will be conducted with individual participants until thematic saturation is reached to offer sufficient insight to help refine the CBTi-CB condition for this study. Interviews will be audiotaped and transcribed. A rapid data analysis process will be utilized; this is a qualitative approach used when there is need for time-sensitive targeted and actionable qualitative information. Intervention development will consist primarily of identifying preferences for content delivery and content via qualitative interviews with participants, and thus will not involve formal statistical inference. We may conduct descriptive analyses of participants' data regarding preferences which, combined with feedback from the field testing, will lead to refinements in the intervention content and delivery.

Specific Aim 1 - Phase 2 (Beta testing). Based on participant feedback and internal advisory group revisions, both treatment manuals (CBTi-CB and SE) will be beta-tested with 8 participants (4 for CBTi-CB and 4 for SE). Following the eligibility consent process, participants in the beta testing phase will be asked to complete a screening survey and a voluntary urine drug screen to confirm eligibility prior to completing other study procedures. Participants will receive $10 in cash or gift cards for completing the survey and drug screen. Participants who do not wish to provide a urine drug screen will not be eligible to participate in the beta testing portion of the project. The drug screen will test for the presence of cannabis, amphetamines, methamphetamines, cocaine, and opioids, as cannabis-only zero exposure urine drug tests are not available, but we will not be recording any drugs other than cannabis. Interested participants who test positive for cannabis and are eligible based on the screening survey will be consented for the full study. They will be asked to complete a baseline health survey and a brief (Timeline Followback, TLFB) interview and will be remunerated $40 in cash or gift card. During the baseline assessment, participants will be given an actigraph watch to wear during their participation in the study. Participants will be given instructions on the operation and care of the device and will be instructed to wear the watch for at least 7 consecutive days. Participants will then be assigned to receive either the CBTi-CB or SE condition, depending on participant gender and date of enrollment. Each condition consists of 6 therapy sessions, each 45-60 minutes in length, designed to be delivered remotely via video chat or telephone once a week over a period of 6-8 weeks post study enrollment. All therapy sessions will be audio recorded. Those participants who do not wish to be audio recorded will not

be eligible to participate. During their participation in the study, participants will be receiving daily e-mails from REDCap instructing them to complete a brief survey regarding their sleep. Participants will have 24 hours from the time the e-mail is sent to complete the survey via REDCap. Following completion of the therapy sessions, participants will be instructed to wear the actigraph watch again for an additional 7 consecutive days before the follow-up assessment will be completed. The follow-up assessment will include a self-report survey, TLFB interview and a semi-structured post-treatment interview, in which participants will be asked to share their impressions of each session (e.g., focused on content, length, personal relevance) and of the overall cohesion across therapy sessions. Participants will also be asked for feedback regarding wearing the actigraph as well as their impressions of completing the daily surveys. At the following up assessment, participants will also be asked to provide a voluntary urine drug screen that will detect only the presence of cannabis. Participants will receive $40 in cash or gift cards for completing the follow-up assessment, and will receive an additional $10 in cash or gift cards for completing the voluntary urine drug screen. In addition, participant will receive a $30 in cash or gift cards to cover costs related to the use of technology for the therapy (e.g. phone minutes or data charges). They will also receive an extra $10 in cash or gift cards if they completed at least of four out of seven daily surveys per week during their study participation. These are the surveys that ask about sleep and cannabis use and are sent to participants daily via email/REDCap. Total compensation for all study activities, including eligibility screening, is $140.

Relevant revisions will be made to the manuals based on feedback generated from the post-treatment follow-up assessment. Following completion of all beta-testing participants, one last meeting will occur between the Internal and External Advisory Groups to discuss the near-final versions of the manuals and to provide the opportunity for any remaining fine-tuning of session content for both conditions prior to the pilot RCT trial.

*Developing training protocols for therapists***.** During the initial phases of the project, we will also refine our therapist training protocols**.** Therapist training will be led by Dr. Conroy and the project coordinator. Dr. Conroy is accredited in Behavioral Sleep Medicine and served as a consultant on the national Veteran's Administration cognitive-behavioral therapy for insomnia training program; thus, she is very experienced in training therapists in CBTi. Therapists will be required to review training manuals in CBTi (e.g., Insomnia: A Clinical Guide to Assessment and Treatment[78], Cognitive-Behavioral Therapy for Insomnia: A Session by Session Guide[79]) as well as the study-specific therapist manuals. Skills training will follow both current CBTi dissemination protocols[80] as well as past experience by the research team, will include activities such as listening to de-identified tapes from prior research protocols demonstrating the therapeutic techniques, role playing, being directly observed by Dr. Conroy while providing CBTi-CB to mock cases and during beta testing. The therapist will also receive training on how to handle potential crisis situations and adverse events. Two masters level therapists will be trained to deliver both interventions (CBTi-CB and SE).

Develop CBTi-CB and SE Integrity and Fidelity measures. With participant permission (>90% in previous work), all therapy sessions will be audio recorded to ensure therapist fidelity to the intervention manuals. The development of the integrity measures will be based on procedures used in Project MATCH[81] and the prior experience of our research group. For each session topic, dichotomous items for therapist adherence will be generated from session outlines and materials to include specific session topics covered. This will produce 6 session-specific *Adherence Rating Scales* for each condition. To produce a *Therapist Skill/Competence Scale* to apply across sessions, Likert items covering general CBTi (e.g., delivery of session rationale in CBTi framework, skill teaching, in session CBTi exercises) therapist behaviors will be generated based on Cognitive Therapy Rating Scale (CTS). Instructions regarding item intent, examples and scoring guidelines will be developed for the Session-Specific Adherence Rating Scales, as well as the Therapist Skill/Competence Scale.

Develop participant process/feedback measures. Participant process/feedback measures will be developed. Participants will be asked for their feedback regarding their experiences in the using a semi-structured post-treatment interview. Participants will be asked to share their impressions of each session (e.g., focused on content, length, personal relevance) and of the overall cohesion across therapy sessions. Questions regarding the acceptability of all study activities will be asked in addition to suggested changes for the future trial. Relevant revisions will be made to the manuals and protocol based on this feedback, and a session feedback form will be created to assess the helpfulness and relevance of session topics.

Specific Aim 2: Conduct a pilot RCT comparing remotely -delivered CBTi-CB to remotely -delivered SE. The second aim of the study is to conduct a pilot randomized trial of CBTi-CB vs. SE (N = 60). This approach is pragmatic and real-world in nature, as both conditions will be delivered remotely to individuals who report using cannabis for insomnia, yet suffer at least mild insomnia. Participants for the RCT phase will be recruited in various ways, including from two Michigan licensed cannabis provisioning centers (OM of Medicine and Bloom City Club), online at UMHealthResearch.org, in the community via flyers, on social media, and at community events. Participants will be randomized to CBTi-CB or SE and undergo self-reported assessments of sleep/insomnia, substance use, and functioning before and after treatment (~8 weeks) and at 16-week follow-up. As many subjects as possible will also undergo objective sleep assessment with actigraphy, if feasible. The ultimate goal is to use this pilot study to provide all of the necessary elements to conduct a future fully-powered RCT comparing these two conditions. To ensure the rigorous conduct of this study, we will utilize the CONSORT checklist and flow diagram to document participant accrual, flow and retention at all stages of the study.

A scale will be developed that includes items assessing non-therapeutic or "contaminating" therapist behaviors (e.g., use of confrontational strategies, blaming); this scale will be a component of the measurement of therapist skill/competence for CBTi-CB and will be the primary measure of therapist skill/competence for SE. Twenty-five percent of session tapes will be double-coded using the Adherence and Competence scales. We have used similar procedures in prior intervention studies, which have resulted in instruments with sound psychometric properties.

Data Analysis. Data will be examined using standard univariate summary measures and bivariate statistical measures of association, as well as graphical displays. Tests for linearity, independence, missingness, and distributional assumptions (e.g., normality) will be conducted on key variables for each assessment. Distributions will be examined to guide modeling decisions.

Consistent with Stage 1B research, the primary goals for the pilot RCT are to obtain information about the feasibility of the proposed RCT and estimate the distribution and variability of primary and potential mechanistic outcomes within intervention and control conditions. Initial analyses will involve calculating the attrition rates for 6- and 18-week follow-up assessments in each study group and identifying predictors of drop-out. We will also quantify session attendance and note the percent of participants who did not complete all sessions to identify ways to decrease drop-out and non-compliance to the intervention. Additionally, we will examine all participant feedback from the *Session Feedback Forms* and descriptive data from the measures of treatment integrity and therapist fidelity measures. To examine treatment integrity and fidelity (*the Session-Specific Adherence Rating Scales* and the *Therapist Skill/Competence scale*), inter-rater reliability will be examined with Yule's Y statistic, by contrasting therapist results with those of the raters, as well as by contrasting those of the two independent raters. The items will be summed to produce overall competency summary scales. Cronbach's alpha will be used to examine the internal consistency of each summary scale separately for the therapist and raters. The items and rating scales (anchors) will be further refined (added, eliminated or modified), if necessary, based on discussion of face validity and analysis of item appropriateness. These items will be used to monitor therapist skill and fidelity to the intervention protocol and to maintain the integrity of the intervention.

The primary outcomes of interest include insomnia severity, functioning, and frequency of cannabis use. Potential mechanisms of the intervention include sleep-related behaviors (e.g., changes in time in bed, regularity of sleep schedules) and sleep-related cognitive factors (e.g., changes in sleep-related beliefs, self-efficacy to manage sleep without cannabis, motivation to use cannabis to manage sleep). Based on recent guidelines for Stage 1B research, we will calculate means and standard deviations for primary and mechanistic measures at baseline, post-treatment, and follow-up, as well as change scores for the CBTi-CB and SE groups. In line with recent recommendations for analysis of data from pilot studies, we will focus on estimation of confidence intervals for between-group differences at baseline and all follow-ups.

Moreover, although we recognize that the proposed project will not have adequate power to serve as a definitive study of intervention effects, to prepare for analyses for the future large-scale definitive trial we will compare the outcomes between the two study groups. We hypothesize that intervention participants will have less severe insomnia, better functioning, and lower frequency of cannabis use at follow-ups. The primary outcomes are hypothesized to meet the assumptions of continuous variables, and we will consequently use t-tests to make comparisons. If, however, the distribution of a measure is skewed, alternative modeling strategies (e.g., Poisson regression) will be used. We will examine separate models by sex (i.e., stratified analyses). We will also conduct exploratory analyses of how potential mediators (e.g., self-efficacy) relate to changes in insomnia and cannabis use, and will examine whether changes in insomnia and cannabis use are correlated. Although our sample size is not sufficient to conduct formal mediation analysis, results will inform the identification of those variables that best capture the mechanisms for intervention effects. We will use an intent-to-treat framework.

HUMAN SUBJECTS CONSIDERATIONS

For all phases of this study, approval will be obtained from the Institutional Review Board at the University of Michigan. This research is also covered by a Certificate of Confidentiality from NIDA.

Specific Aim 1-Phase 1: Qualitative Interviews

Recruitment Procedures. Individuals who report cannabis use for insomnia, and suffer at least mild insomnia will be recruited from medical marijuana certification clinics and Michigan licensed marijuana dispensaries. Clinics and dispensaries are generally open during regular business hours and have designated waiting rooms in which individuals can be approached. Individuals ≥21 years of age will be approached by research staff in the waiting room at the clinic sites and recruited for the qualitative interview portion of the study. All potentially eligible individuals in the waiting rooms of the study sites on days of active recruitment will be invited to learn about the study and participate in eligibility screening. Research staff will follow the recruitment script which includes questions to determine eligibility. Written informed consent will be obtained from those who are eligible and agree to be interviewed.

The project staff will conduct 10 qualitative interviews with participants recruited from the study sites who use cannabis for insomnia (men: n=5; women: n=5) to better understand these individuals' perceptions of the relationships among insomnia, coping, functioning and cannabis use as well as what might influence adherence to a 6-session telehealth intervention. These qualitative interviews will allow for feedback on the potential content of initial drafts of the CBT for insomnia for adults who use cannabis (CBTi-CB) and Sleep Education Control (SE) manuals. Participants will be remunerated $50 for participation in the qualitative interviews, which will be audio-recorded (with permission) and may take place in person or over the phone

Informed consent. We request a waiver of informed consent to ask eligibility screening questions to potential participants as part of the recruitment process. No names or identifying information will be collected from individuals who are not eligible or choose not to participate in the study. Written informed consent will be obtained from eligible and interested participants. All participants will be told that participation is voluntary, that

they can withdraw at any time, and that this will not impact any aspect of the treatment they receive at the clinics or dispensaries. The limits of the Certificate of Confidentiality are explained in the consent form but study staff will also verbally explain the limits of confidentiality. The qualitative interviews will commence after the participants provide written informed consent. When providing written informed consent, participants will be given a copy of the consent form to keep.

Study Eligibility Criteria

The ***inclusion criteria*** are: (1) age ≥ 21; (2) Insomnia Severity Index (ISI) score >10, indicative of at least "mild" insomnia; (3) use of cannabis once a week during the past 3-months; (4) self-reported use of cannabis to manage insomnia at least once in the past week.

The ***exclusion criteria*** are: (1) individuals who do not understand English; (2) individuals judged unable to provide informed consent (e.g., intoxication, mental incompetence); (3) self-reported cancer; and (4) self-reported pregnancy.

Justification for selection criteria. Participants in this study will be 21 years old and older for several reasons. First, although state law does allow individuals under the age of 18 to obtain cannabis for medical purposes with consent of a legal guardian, available data indicate that very few adolescents have been issued medical cannabis cards in Michigan. In addition, with the new recreational marijuana laws allowing non-medical use of cannabis, we are not solely recruiting medical cannabis users. This new law states all recreational marijuana uses must be 21 years or older to possess or use marijuana. Therefore, all participants should be age 21 years or older to follow Michigan recreational marijuana laws.

In order to collect interview data from a sample that will be representative of the population to be recruited for the beta testing and RCT, we will exclude those with self-reported cancer or pregnancy. Individuals who use marijuana for cancer may experience a different trajectory than those who are not and women who self-report that they are pregnant will be excluded because: (a) of the potential risks of study participation to pregnant women; and (b) we are unlikely to have sufficient numbers of pregnant women to facilitate meaningful subgroup analyses.

Potential Risks, Minimizing Risks, and Potential Benefits

1. Potential Risks

a. Loss of Confidentiality

The major potential risk to study participants is violation of confidentiality of interview data. The risk of violation of confidentiality exists because participants will be disclosing personal information in interviews. This risk is related to the damage that could be caused by an inadvertent release of sensitive information (e.g., substance use, medical conditions). Participants will be informed of the procedures taken to protect their confidentiality.

b. Discomfort During Interview

There is also a slight risk of psychological discomfort to study participants as a result of being asked personal questions on sensitive topics. Participants may also become anxious or upset during discussions of their thoughts about managing their insomnia or substance use during the interview.

2. Minimizing risk

a) Loss of confidentiality (risk unlikely) To minimize the violation of confidentiality, we will ensure that data are protected and cannot be linked to a particular person. Unique identification numbers will be assigned to each

participant and all forms are coded with this number, rather than by name. All data are stored in locked file cabinets. Consent forms and subject code/name sheets will be stored separately, because they contain identifying information. Data entry staff will work with forms that contain only subject numbers. Physical security of data will be assured by daily and weekly back-ups. For each stage of the proposed research investigation, participants' names and contact information will be stored in a secure, password-protected database, separate from their study data and only accessible to members of the research team for research purposes. Paper copies of signed consents and completed contact information forms will be stored in locked file cabinets only accessible to study staff, separate from study data. Names will be linked to individual ID numbers only in a study crosswalk database, which will be kept in a restricted access folder on a secure server and destroyed at study completion. Finally, when making telephone calls to contact subjects, we will contact only the subject and those people for whom the subject has provided written authorization.

Data will be collected only with written informed consent from the participant. With participant permission, qualitative interviews will be audio-recorded for transcription and analysis, and may take place in person or over the phone. The audio-recordings of the interviews will be destroyed after the files are uploaded to a password-protected, secure server with restricted access. Participants will be asked not to mention names or other identifying information in during the recorded interview. Any identifying information will be removed from transcriptions. Once collected, participant data will remain confidential. Only study team members who have completed appropriate training in the protection of human subjects at the University of Michigan will have access to the data. Hard copies of data will be stored in a locked data storage room in the North Campus Research Complex at the University of Michigan. Electronic data will be stored on a secure computer on password-protected files and coded by subject identification number so that participants cannot be identified by their research record. Any data collected via pen and paper, such as tracking forms, will be manually entered using double entry when possible. Data cleaning will be conducted throughout the data collection period to ensure the production of a final dataset for analysis at the end of data collection.

b) Discomfort during assessments (risk likely):

Participants may become upset, anxious, or uncomfortable as a result of being asked very personal questions. To minimize this risk, all interviews will be conducted in private offices with skilled research staff. Research assistants will be trained to respond to this emotional distress and to refer participants to appropriate resources as necessary. Specifically, this training will include information regarding evaluating warning signs of distress that could occur as a result of the screening, intervention, or assessments, and means of addressing such issues and minimizing distress. Such strategies will include maintaining an empathic response, acknowledging the distress through reflection, avoiding blame, processing in a non-blaming non-confrontational manner, and eliciting or encouraging use of relaxation and cognitive calming strategies. Crisis procedures, effective in previous projects conducted by the study investigators, will also be utilized, including immediately paging Drs. Ilgen or Arnedt (Multiple PIs) for consultation. If any research staff observes any indication of potential distress, including through review of responses to the assessments, further evaluation of the participant will be conducted by a licensed clinician. All participants are free to terminate the interview at any time or refuse to respond to any question. As with any research project, unexpected events are always possible. If risk is determined to be present, we will implement our standard clinical protocol for responding to suicide risk. Ongoing follow-up will occur until it is determined that risk is minimal.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

Subjects who participate in this qualitative interview phase of the proposal may experience the benefits of catharsis, self-acknowledgment, and self-awareness when disclosing personal information related to their experiences of chronic insomnia and of seeking cannabis for the treatment of chronic insomnia. Study staff conducting the qualitative interviews will be trained to be empathic and reflect back what they have heard from

participants. This could have benefits that are similar to an unstructured supportive psychotherapy session. Participants may also benefit from the knowledge that they are contributing to the development of a treatment for a condition that is highly comorbid with the use of cannabis.

4. Importance of the Knowledge to be Gained

The risks to subjects associated with participating are reasonable compared to the potential knowledge to be gained. Identifying an effective and safe non-medication treatment for insomnia, a highly common co-occurring condition in this population of individuals seeking cannabis, could improve nighttime and daytime symptoms and reduce cannabis use. The application takes a pragmatic approach to cannabis use to investigate whether this approach can help adults who use cannabis to function better and use less cannabis.

Specific Aim 1-Phase 2: Beta Testing

Recruitment Procedures. Participants for the beta testing phase will be recruited from two Michigan licensed cannabis provisioning centers (OM of Medicine and Bloom City Club). These cannabis provisioning centers (also known as dispensaries) are generally open during regular business hours have waiting areas in which individuals can be approached. All potentially eligible individuals in the waiting rooms of the study sites on days of active recruitment will be invited to learn about the study and participate in eligibility screening. Research staff will follow the recruitment script. Written informed consent will be obtained from those who are interested and agree to participate. After collecting the informed consent, the eligibility screening survey will be administered. Since recruitment will occur in a waiting room of the dispensary, participants will be asked to complete the eligibility questions via a brief tablet screen (or paper version if the participant desires) to ensure their answers will be kept private. If participants screen eligible via the survey, they will be asked to take a urine drug screen to detect THC. If a participant declines to provide a urine sample, or if the results of the urine drug screen are negative for the presence of THC, they will be excluded from participating further. Participants will be given a small bag containing the test kit to take into a restroom at the recruitment site. For participants who are unable or unwilling to provide a urine sample at the recruitment site, they may be given the option to complete the urine screen at a separate location (e.g. in the community or at the research office) or at their homes. The urine drug screen will provide information regarding recent use for opioids, cannabis, amphetamines, methamphetamines, and cocaine, but only cannabis use will be recorded.

Those who are not eligible will be thanked for their time. Individuals who meet eligibility (individuals who report cannabis use for insomnia, suffer clinically significant insomnia, and have a positive urine drug screen for THC) based on their answers and urine drug screen will be invited to participate in the full study. Participants will be paid $10 cash or gift card for completing the eligibility survey.

Eligible participants will be invited to participate in the full study, involving a separate consent form. Following the completion of the written informed consent for the full study, participants will be asked to complete the baseline assessment. Baseline assessments will include both a tablet-based survey (or paper/pencil version based on participant preference) and a researcher administered TLFB interview. These assessments will gather detailed evidence of problems related to sleep, frequency of recent substance use including cannabis use, substance use consequences, depression and self-efficacy. Because we will need to contact participants for completion of the daily surveys, therapy sessions, and follow-up assessments, the research staff member will collect detailed locator information. This information will include the participant's phone number(s), address(es), e-mail addresses, and contact information for family members/friends who would know how to reach them. Participants will also be able to contact study staff or correspond/receive appointment reminders through text. Because participants will complete several assessments remotely, we will set up a secure study e-mail account to be used for participants to contact study staff or for study staff to send appointment reminders and surveys to participants. The e-mail address is: UM-CannSleep@med.umich.edu.

Following the administration of study measures, the participants will be provided with an actigraphsleep monitoring watch The actigraph (Actiwatch Spectrum Plus, Philips Respironics, Murrysville, PA) is a small waterproof device the size of wrist watch (48 mm x 37 mm x 15 mm weighing 31 grams) that is meant to be worn continuously on the non-dominant wrist. An accelerometer integrates movement frequency and intensity into a single measurement. In addition, a photodiode sensor continuously monitors incoming light and stores the data in lux levels. The actigraphs are set at a sampling rate of 30 seconds. Activity and light data are downloaded to computer and sleep/wake activity is estimated using Actiware® – Sleep software and following published guidelines. Data is accessed through the Actiware® – Sleep software and is identified by study participation ID. Participants will be asked to wear the actigraphy activity tracker for one-week (at least 7 consecutive days) post-enrollment and again for at least one-week post-treatment (at approximately 6 weeks post-enrollment). Watches will be returned to the study team after the first 7 days of wear, returned to the participant after the last therapy session, and collected by the study team at the follow up assessment. To do so, we will ask participants to either 1. send the actigraphy activity tracker back in the mail using a prepaid envelope, 2. leave it in a drop box located at the recruitment sites, or 3. have study staff meet the participant at home or in the community to pick up or drop off the actigraphy activity tracker. Participants will be asked to wear the watch for at least 7 days post-treatment and will return the watch at their in-person follow up or via mail after their electronic/mailed follow up is completed. Actigraphy activity trackers will come with informational brochures from the Philips Respironics company and pre-paid return envelopes for the participants to mail them back after both baseline and post-treatment assessment time points. Once the participant completes the survey, research staff will review the survey prior to the participant leaving the room to assess for risk status.

Follow-up assessments will be conducted in person in the community or in our offices at the University of Michigan, or via emails containing REDCap survey links or mailed paper surveys where participants can complete surveys on their own. For those assessments that occur in the community, research staff will arrange to meet participants at a convenient and confidential location in the community (e.g., a local library, their home). If we interview a participant in his/her home, we will arrange for a second research staff member to go along for staff safety reasons. We have used this process successfully in our prior work with adults with SUD.

Data Collection: Assessment content will measure demographic characteristics, reasons for seeking cannabis and current uses (must include insomnia), frequency and severity of insomnia, and presence of co-occurring exclusionary medical/psychiatric conditions, and other sleep disorders. The screening assessment will include questions that will allow for determination of eligibility. Baseline assessments are intended to confirm eligibility and assess the acceptability of the measures used that will obtain greater detail about sleep, functioning, substance use and the proposed mechanisms of change in our theoretical model in our next phase. Data will be collected via emailed surveys, tablets, paper, actigraphy, and urine drug screens.

Specimens: In this study, we will be collecting urine to analyze for recent cannabis use. We will be using urine testing kits that give immediate results; therefore, the study staff will be conducting the sample testing and no labeling or storage will be necessary. Participants will be given a small bag containing the test kit to take into a restroom, either at the recruitment/follow up site or at home. Once the specimen has been provided in the test cup, the participant will either return the bag to the research staff member for immediate testing or send a picture of the results to the secure study email, if they prefer to take the drug screen at home. Research staff will record test results. After testing is complete, the urine sample will be discarded by flushing it down the toilet if done in person. No identifying information will be marked on the testing container. The validity of self-report of cannabis use may be increased when a urine drug screen is performed. The urine drug screen will provide information regarding recent use for THC only, for eligibility confirmation. Specimens will be collected in a specimen container about 4 oz. in size, although only a minimal amount of urine is needed.

Assessment Instruments	Screening/ Eligibility	Baseline	Before and/or	Post-Intervention (~6 weeks)	Follow Up

			after session		
Demographics	X				
Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)	X				
Fagerstrom Test (for nicotine dependence)	X				
Fagerstrom Test (for cannabis dependence)	X				
Cannabis Use Disorder Identification Test (CUDIT)	X				
Perceived Relief (PR)	X				X
STOP-BANG (Obstructive Sleep Apnea measure)	X				
Restless Leg Syndrome Questionnaire (RLSQ)	X				
Insomnia Severity Index (ISI)	X				X
Urine Drug Screen (THC only)	X				X
Generalized Anxiety Disorder 7 Item (GAD-7)		X			
Personal Health Questionnaire Depression Scale (PHQ-8)		X			
The Revised Behavior and Symptom Identification Scale (BASIS-R)		X			
12-Item Short Form Health Survey (SF-12)		X			X
Timeline Follow Back		X			X
Modified Self Efficacy Scale (SES)		X			X
Dysfunctional Beliefs About Sleep (DBAS-16)		X			X
Substance Use Sleep Scale (SUSS)		X			X
Modified Marijuana Motives Questionnaire (MMQ)		X			

Medical Marijuana Use		X			
Prescription Misuse (BOYD)		X			X
Cannabis Expectancy Questionnaire (CEQ)		X			X
Side Effect Checklist (SECL)		X			X
Marijuana withdrawal checklist revised (MWC-R)		X			X
PEG Three-item Scale Assessing Pain Intensity and Interference		X			X
BRFSS Model 16(Marijuana Use Type)		X			X
Multidimensional Fatigue Inventory (MFI-20)		X			X
Epworth Sleepiness Scale		X			X
Therapy Evaluation Questionnaire		X			X
Daily Sleep/Wake Diary		X	X	X	X
Actigraphy		X		X	X
Session Attendance			X	X	

Primary outcomes: These assessments will not be used to assess outcomes but rather to test feasibility and acceptability. With participant permission, qualitative interviews, therapy sessions and the follow-up interview will be audio-recorded to ensure therapist fidelity to the intervention and for transcription of the interviews. Using a semi-structured post-treatment interview guide, participants will be asked to share their impressions of each session (e.g., focused on content, length, personal relevance) and of the overall cohesion across therapy sessions. We will also be asking about acceptability for participation in all study activities, and for any suggested changes for the future trial. Relevant revisions will be made to the manuals and protocol based on this feedback.

All remuneration for the study will be in the form of gift cards or cash. Participants will be remunerated with a $40 for the completion of baseline assessment, $40 for completion of the follow-up assessment, $10 for completing four out of seven days of the daily online survey for every week enrolled in the study, plus an additional $10 incentive for a urine drug screen at follow up. Participants will also receive $30 to compensate them for any potential charges related to the use of their technology. Participants who do not complete all therapy sessions will still receive the $30 to cover technology costs, however, they must have completed at least one phone session.

Informed consent. Trained research staff will conduct the informed consent process. This phase of the study will have a 2-part consent process. First, an eligibility consent will be completed in order for participants to complete the screening survey and urine screen. Second, those who are eligible and interested will complete a second consent document explaining the full study. Individuals interested in participating in the study will review the consent with the research staff. All participants will be told that participation is voluntary, that they can withdraw at any time, and that this will not impact any aspect of the services they receive at the clinics or dispensaries, including their ability to receive cannabis. After reviewing the consent form, research staff will ask the patient if he/she has any questions regarding their participation or the study requirements and limitations. The limits of the Certificate of Confidentiality are explained in the consent form, but study staff will also verbally explain the limits of confidentiality. Any patients who request more time to review the consent form or consult with others will have the opportunity to do so. These patients will have the opportunity to have research staff contact them at a later time or to contact research staff themselves. Those interested in participating will be asked to sign the consent form. When providing written informed consent, participants will be given a copy of the consent form to keep and the original will be filed in a confidential research file. Study staff will review the consent form for accuracy and completeness before beginning any study procedures.

Study Eligibility Criteria.

Inclusion criteria. (1) age $\geq$ 21 or older; (2) Insomnia Severity Index (ISI) score >10, indicative of at least "mild" insomnia; (3) use of cannabis three times a week within the past three months; (4) self-reported use of cannabis to manage insomnia at least once a week over the past month; (5) consistent access to a telephone, smartphone, laptop, or tablet; and (6) a positive urine drug screen for THC.

Exclusion criteria. (1) individuals who do not understand English; (2) individuals judged unable to provide informed consent (e.g., intoxication, mental incompetence); (3) diagnosis or high suspicion of a sleep disorder other than insomnia based on validated self-report measures; (4) self-reported cancer; (5) self-reported pregnancy; and (6) self-reported rotating or night (3rd) shift work. Participants will not be excluded if they are taking prescription or over the counter medications for sleep, however they will need to report being stable on the medications for at least 8 weeks and agree to maintain the same regime throughout the study. Those who have been taking prescription medications for sleep for less than 8 weeks, or who report they are unable to continue with their medications for the duration of the study (approximately 10 weeks) will be excluded.

Justification for selection criteria. Participants in this study will be 21 years old and older for several reasons. First, although state law does allow individuals under the age of 18 to obtain cannabis for medical purposes with consent of a legal guardian, available data indicate that very few adolescents have been issued medical cannabis cards in Michigan. In addition, with the new recreational marijuana laws allowing non-medical use of cannabis, we are not solely recruiting medical cannabis users. This new law states all recreational marijuana uses must be 21 years or older to possess or use marijuana. Therefore, all participants should be age 21 years or older to follow Michigan recreational marijuana laws.

In order to collect interview data from a sample that will be representative of the population to be recruited for the RCT, we will exclude those with self-reported cancer or pregnancy. Individuals who use marijuana for cancer may experience a different trajectory than those who are not and women who self-report that they are pregnant will be excluded because: (a) of the potential risks of study participation to pregnant women; and (b) we are unlikely to have sufficient numbers of pregnant women to facilitate meaningful subgroup analyses.

Access to a smartphone, computer, or tablet is required to deliver intervention sessions, as all sessions are meant to be delivered remotely via BlueJeans video chat or telephone. Those who do not report having reasonable access to the technology needed for the study will be excluded.

Potential Risks, Minimizing Risks, and Potential Benefits

1. Potential Risks

a. Loss of Confidentiality

The major potential risk to study participants is violation of confidentiality of survey and interview data. The risk of violation of confidentiality exists because participants will be disclosing personal information in surveys and interviews. This risk is related to the damage that could be caused by an inadvertent release of sensitive information (e.g., substance use, medical conditions). Participants will be informed of the procedures taken to protect their confidentiality.

b. Discomfort During Interview

There is also a slight risk of psychological discomfort to study participants as a result of being asked personal questions on sensitive topics. Participants may also become anxious or upset during discussions of their thoughts about managing their insomnia or substance use during the interview.

2. Minimizing risk

a. Loss of confidentiality (risk unlikely)

To minimize the violation of confidentiality, we will ensure that data are protected and cannot be linked to a particular person. Unique identification numbers will be assigned to each participant and all forms are coded with this number, rather than by name. All data are stored in locked file cabinets. Consent forms and subject code/name sheets will be stored separately, because they contain identifying information. Data entry staff will work with forms that contain only subject numbers. Physical security of data will be assured by daily and weekly back-ups. Data cleaning will be conducted throughout the data collection period to ensure the production of a final dataset for analysis at the end of data collection.

Study data will be collected and managed using REDCap (Research Electronic Data Capture). Participants' names and contact information will be stored in a secure, REDCap database, separate from their study data and only accessible to members of the research team for research purposes. REDCap is a secure web application designed to support data capture for research studies. It provides userfriendly web-based case report forms, real-time data entry with branching logic and validation (e.g. for data types and range checks), audit trails, a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus), procedures for importing data from external sources, and advanced features such as a data quality check module. The system was developed by a multiinstitutional consortium initiated at Vanderbilt University. REDCap servers are physically located in the University of Michigan Medical School Information Systems (MSIS) data center. Application and database servers are on virtual machines (VM). The VM servers are Red Hat Enterprise Linux Server 5.6 (64-bit, 2.6.18 238 e15-smp kernel) 2x AMD Opteron 6174 5.0.95 2.2 GHz with 4 GB RAM, running Apache 2.2.3 (application servers) and MySQL (database servers). Physical security for the databases is provided in a professionally managed and equipped tier-2 data center with tightly controlled access. Remote data access employs SSL encryption and 2-tier Kerberos/Level 1 and UMHS Level 2 password challenges via LDAP authentication. Access to the application, the database, and the underlying systems infrastructure are consistent with industry best practices including HIPAA security and privacy requirements and the HITECH Act. The application provides audit trails on user access to MICHR and MSIS technical and support teams. Backup of data is managed by MSIS and vulnerability testing is performed regularly by the University of Michigan Health
System Medical Center Information Technology. Risk evaluation is performed using a methodology derived from NIST Special Publication 800-53 – "Recommended Security Controls for Federal Information Systems" and is used to refine and improve operating policies and procedures. Daily backups and VM snapshots of the application and database servers are stored on a remote storage device. The restoration of the servers from a hardware or software failure are protected for 24 hours of disaster recovery.

Interviews will be audio-recorded for transcription and analysis, and may take place in person, via an online

video chat (BlueJeans), or over the phone. The intervention sessions will be remotely delivered via telephone or BlueJeans video conferencing (https://www.bluejeans.com/). BlueJeans provides a cloud-based audio/video/content-sharing conferencing service. The service is vendor-agnostic and allows up to 150 endpoints to connect for a meeting. U-M's current contract with BlueJeans enables all U-M faculty, staff, and students to register for a BlueJeans User Account. BlueJeans collects and maintains data related to the date, time, and attendees of a meeting. Actual video or audio content is only stored by BlueJeans when the meeting host turns on the recording feature. We will not be using the recording feature on Bluejeans. U-M's agreement with BlueJeans includes a Business Associate Agreement. This means individuals may use this service to share Protected Health Information (PHI) regulated by HIPAA. For more information, BlueJeans Security and Privacy agreements with the University of Michigan can be found at https://safecomputing.umich.edu/dataguide/?q=node/181. The audio recordings for the interviews will be done with a digital voice recorder. The audio-recordings of the interviews will be destroyed after the files are uploaded to a password-protected, secure server with restricted access. Participants will be asked not to mention names or other identifying information in during the recorded interview. Any identifying information will be removed from transcriptions.

We have set up an email account to be used for subjects to contact study staff or for study staff to send appointment reminders and online surveys (via REDCap) to subjects. The e-mail address is: UM-CannSleep@med.umich.edu.

b) Discomfort during assessments (risk likely):

Participants may become upset, anxious, or uncomfortable as a result of being asked very personal questions. To minimize this risk, all interviews will be conducted in private offices with skilled research staff. Research assistants will be trained to respond to this emotional distress and to refer participants to appropriate resources as necessary. Specifically, this training will include information regarding evaluating warning signs of distress that could occur as a result of the screening, intervention, or assessments, and means of addressing such issues and minimizing distress. Such strategies will include maintaining an empathic response, acknowledging the distress through reflection, avoiding blame, processing in a non-blaming non-confrontational manner, and eliciting or encouraging use of relaxation and cognitive calming strategies. Crisis procedures, effective in previous projects conducted by the study investigators, will also be utilized, including immediately paging Drs. Ilgen or Arnedt (Multiple PIs) for consultation. If any research staff observes any indication of potential distress, including through review of responses to the assessments, further evaluation of the participant will be conducted by a licensed clinician. All participants are free to terminate the interview at any time or refuse to respond to any question. As with any research project, unexpected events are always possible. If risk is determined to be present, we will implement our standard clinical protocol for responding to suicide risk, including giving participants a resource brochure. Ongoing follow-up will occur until it is determined that risk is minimal.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

It is believed that research participants may be helped by participating in this study. Participants who receive the CBTi-CB intervention will receive a therapeutic intervention aimed to improve their insomnia symptoms and related functioning during the day. CBT for insomnia has known risks associated with its use, but these are usually tolerable and subjects may not otherwise receive treatment for insomnia. Thus, the risks associated with participating are reasonable in light of the potential benefits to the participating subjects and others. The information control condition represents an increased (enhanced) level of care from standard medical cannabis treatment provided at clinics.

4. Importance of the Knowledge to be Gained

The risks to subjects associated with participating are reasonable compared to the potential knowledge to be gained. Identifying an effective and safe non-medication treatment for insomnia, a highly common co-occurring condition this population of individuals seeking cannabis, could improve nighttime and daytime symptoms and reduce cannabis use. Our study would be the first to evaluate a highly effective sleep-focused intervention and determine the effects on cannabis use in a non-treatment seeking population.

Specific Aim 2: Conduct a pilot RCT comparing remotely -delivered CBTi-CB to remotely -delivered SE.

Recruitment Procedures. Participants for the RCT phase will be recruited in various ways, including in-person from two Michigan licensed cannabis provisioning centers (OM of Medicine and Bloom City Club), online at UMHealthResearch.org, in the community via flyers, on social media via Facebook and Instagram adds run by MICHR, and at community events. The cannabis provisioning centers (also known as dispensaries) are generally open during regular business hours and have waiting areas in which individuals can be approached. All potentially eligible individuals in the waiting rooms of the study sites on days of active recruitment will be invited to learn about the study and participate in eligibility screening. Participants who learn of the study through UMHealthResesearch.org will be contacted after matching with the project or indicating their interest in participating. Participants who learn of the study in the community via flyers and/or community events will reach out to staff or the UMHealthResearch.org site to learn more and will be followed up with via the website, email, or phone. A REDCap link to the screening survey will be available on paper flyers and via UMHealthResearch.org. A Facebook and Instagram paid, targeted ad (created by MICHR) will be pushed from the U-M Health Research Facebook page. This ad will be monitored by MICHR and study team. The MICHR Facebook page is entitled, Michigan Institute for Clinical & Health Research (MICHR).

When enrolling participants in person or explaining the study via phone, research staff will follow the recruitment script. To enhance confidentiality and minimize the collection of identifying information about individuals who do not participate in the study, screening consent will be administered online or on study provided tablet computers as the first page of the screening survey (a waiver of documentation of informed consent for screening is requested). Since recruitment will occur online, in a waiting room of a dispensary, in the community, or at other UM locations, participants will be asked to complete the eligibility questions via a brief tablet screen (or paper version if the participant desires) or via online REDCap survey link to ensure their answers will be kept private. Prospective participants that use the online screening process will enter the survey portal from a link provided in the recruitment ad (paper or electronic) directing them to the UMHealthResearch.org site, where a link for the survey will be available. After clicking the survey link, they will then be asked to review and give e-consent to the short screening survey. During initiation of the screening survey each participant will be assigned a unique respondent ID number by REDCap. Participants will give consent by checking a box on the electronic consent form and will self-administer a screening survey. In the event of technological issues with study tablets or internet service, or participant preference, verbal consent may be obtained for screening and paper/pencil surveys completed. Following determination of eligibility, negative screens will receive a thank you page asking for a phone number or email address to be sent their gift card and ending their participation. The only identifying information collected from those who complete the online screening assessment and are ineligible or choose not to participate in the study will be an email address or phone number, to text or email Amazon gift card codes for screening assessment remuneration. This information will be deleted from the REDCap survey database after participants are sent their e-gift card. Those who are not eligible will be sent the e-gift card and thanked for their time.

If participants screen eligible via the survey and were screened in person, they will be immediately asked to take a urine drug screen to detect THC and other illicit drug use. If participants are screened eligible via the survey and were screened online and are interested in participating further, they will be asked to provide their name, email address, and phone number for scheduling purposes. Study staff will reach out to eligible participants to schedule the urine drug screen and baseline assessment. This appointment can take place in person (when allowed) or online via video chat (BlueJeans, Skype for Business, or Zoom through the

University of Michigan) or by phone. If a participant declines to provide a urine sample or contact information to schedule a time for the urine drug screen and baseline, or if the results of the urine drug screen are negative for the presence of THC, they will be excluded from participating further. Participants will be given a small bag containing the test kit to take into a restroom at the recruitment/enrollment site(s). For participants who are unable or unwilling to provide a urine sample at the time of screening site, they may be given the option to complete the urine screen at a separate location (e.g. in the community or at the research office) or at their homes. As another option for those interested, especially with regard to COVID-19 pandemic risks, a urine drug screen will be mailed to the preferred address given by the participant. Research staff will use a video chat platform (BlueJeans, Skype for Business, or Zoom through the University of Michigan) to call the participant at the scheduled time, explain the urine drug screen to the participant, and ask them to go off camera to use the test. They will be asked to bring the test back to the video chat and show the results to the research staff on the call. This way, it is more likely the actual participant is the one using the urine drug screen. If the participant is unable to video chat with staff, they may send a picture of the urine drug screen results to the study email. The urine drug screen will provide information regarding recent use for opioids, cannabis, amphetamines, methamphetamines, and cocaine. Individuals who meet eligibility (individuals who report cannabis use for insomnia, suffer clinically significant insomnia, and have a positive urine drug screen for THC) based on their answers and urine drug screen will be invited to participate in the full study. Participants will be paid $10 cash, gift card, or e-gift card for completing the eligibility survey.

Eligible participants will be invited to participate in the full study, involving a separate consent form. Potential participants will be asked to provide written (in-person recruitment) or verbal (remote recruitment) informed consent to the full study. Participants recruited remotely will be emailed or texted a copy of the consent form and research staff will review it with the them. Following the completion of the informed consent process for the full study, participants will be asked to complete the baseline assessment. Baseline assessments will include both a tablet/online-based survey (or paper/pencil version based on participant preference) and a researcher administered TLFB interview. Those who give verbal consent will continue by completing the locator form and Timeline Follow Back interview over video chat. These assessments will gather detailed evidence of problems related to sleep, frequency of recent substance use including cannabis use, substance use consequences, depression and self-efficacy. Because we will need to contact participants for completion of the daily surveys, therapy sessions, and follow-up assessments, the research staff member will collect detailed locator information. This information will include the participant's phone number(s), address(es), e-mail addresses, and contact information for family members/friends who would know how to reach them. Participants will also be able to contact study staff or correspond/receive appointment reminders through text. Because participants will complete several assessments remotely, we will set up a secure study e-mail account to be used for participants to contact study staff or for study staff to send appointment reminders and surveys to participants. The e-mail address is: UM-CannSleep@med.umich.edu.

Following completion of data collection during the baseline assessment, participants will be randomized to a treatment condition – Sleep Hygiene Education (SHE; n=30) or Cognitive Behavioral Therapy for adults who currently use cannabis for insomnia (CBTi-CB; n=30). Randomization to condition will be carried out blocking on gender (male versus female). Participant responses to questions based on gender obtained during baseline will be utilized to select the appropriate block for randomization. Research staff will confirm the participant responses before beginning the randomization procedures. "Gender" for randomization purposes will be operationalized as the gender the participants indicated they were assigned at birth; however, additional questions regarding the gender the participant identifies with will also be collected. Should a participant decline to answer a key blocking variable during the survey administration, research staff will verbally ask clarification questions to determine block assignment. If a participant refuses to provide information that allows for the possibility of blocking they will be excluded from participating further in the study.

Computerized randomization will occur in blocks of randomly chosen sizes in order to equalize randomization over time and to prevent the possibility that staff could unwittingly manipulate subject assignment to conditions. The study biostatistician will complete the treatment allocation sequence process prior to the start of

recruitment for the study. Staff members who will be involved in the enrollment process will not be included in the randomization sequencing process. To further avoid manipulation of condition, randomization will not be determined until after all baseline data collection activities have been completed. We will utilize allocation concealment procedures to ensure that that research staff member enrolling the participant will not know in advance which treatment the next person will receive.

Once generated, documents that include the randomization sequence will be password protected to avoid inadvertent access by research staff involved in the enrollment process. The treatment condition assignments will be sealed in envelopes according to the allocation sequence by either the project coordinator or the study data manager prior to the beginning of study recruitment. The randomization process will be overseen by our study data manager and the project coordinator will be notified of assigned condition for specific participants at the completion of all baseline assessments (by opening sealed envelopes). Randomization should occur at the baseline enrollment appointment. Initiation of the study treatment condition (either CBTI-CB or SHE) should take place within one week of study enrollment and randomization in order to provide enough time for all sessions to be completed within the 6-8-week treatment window.

Following randomization, the participants will be provided with an actigraph sleep monitoring watch if it is deemed safe by investigators and the University of Michigan Office of Research (UMOR). By “safe,” we mean that the risk of transmitting COVID-19 via the actigraphy watches or by going into the office to mail/pick up/configure watches is very low. This risk level is likely to change during the course of the study, and decisions will be made on a case by case basis at enrollment. Participants who are given the option to participate in actigraphy sleep data capture will have the option to decline and still participate in the full study. The actigraph (Actiwatch Spectrum Plus, Philips Respironics, Murrysville, PA) is a small waterproof device the size of wrist watch (48 mm x 37 mm x 15 mm weighing 31 grams) that is meant to be worn continuously on the non-dominant wrist. An accelerometer integrates movement frequency and intensity into a single measurement. In addition, a photodiode sensor continuously monitors incoming light and stores the data in lux levels. The actigraphs are set at a sampling rate of 30 seconds. Activity and light data are downloaded to computer and sleep/wake activity is estimated using Actiware® – Sleep software and following published guidelines. Data is accessed through the Actiware® – Sleep software and is identified by study participation ID. Participants will be asked to wear the actigraphy activity tracker for one-week (at least 7 consecutive days) post-enrollment, for at least one-week post-treatment (at approximately 8 weeks’ post-enrollment), and at least one-week pre final follow up (at approximately 16 weeks’ post-enrollment). Watches will be returned to the study team after the first 7 days of wear, returned to the participant after the last therapy session, collected by the study team at the follow up assessment, returned to the participant approximately 1 week before the final follow up assessment, and collected by the study team at that final assessment. To do so, we will ask participants to either 1. send the actigraphy activity tracker back in the mail using a prepaid envelope, 2. leave it in a drop box located at some of the recruitment sites, or 3. have study staff meet the participant at home or in the community to pick up or drop off the actigraphy activity tracker. Participants will be asked to wear the watch for at least 7 days post-treatment and again for at least 7 days pre- final follow up, and will return the watch at their in-person follow up or via mail after their electronic/mailed follow up is completed. Actigraphy activity trackers will come with informational brochures from the Philips Respironics company and pre-paid return envelopes for the participants to mail them back after both baseline and post-treatment assessment time points. Once the participant completes the survey, research staff will review the survey prior to the participant leaving the room to assess for risk status.

Follow-up assessments will be conducted in person in the community, in our offices at the University of Michigan, or via emails containing REDCap survey links or mailed paper surveys where participants can complete surveys on their own. For those assessments that occur in the community, research staff will arrange to meet participants at a convenient and confidential location in the community (e.g., a local library, their home). If we interview a participant in his/her home, we will arrange for a second research staff member to go along for staff safety reasons. We have used this process successfully in our prior work with adults with SUD. For surveys that are taken online, appointments will be scheduled with participants for research staff to contact

them via a video chat platform (BlueJeans, Skype for Business, or Zoom through the University of Michigan) or via phone to complete the TLFB interview.

Data Collection: Assessment content will measure demographic characteristics, reasons for seeking cannabis and current uses (must include insomnia), frequency and severity of insomnia, and presence of co-occurring exclusionary medical/psychiatric conditions, and other sleep disorders. The screening assessment will include questions that will allow for determination of eligibility. Baseline assessments are intended to confirm eligibility and collect data on participants' sleep, functioning, and substance use. Data will be collected via emailed surveys, tablets, paper, actigraphy, and urine drug screens.

Specimens: In this study, we will be collecting urine to analyze for recent cannabis and other illicit drug use. The urine drug screen will provide information regarding recent use for opioids, cannabis, amphetamines, methamphetamines, and cocaine. We will be using urine testing kits that give immediate results; therefore, the study staff will be conducting the sample testing and no labeling or storage will be necessary. Participants will be given a small bag containing the test kit to take into a restroom, either at the recruitment/follow up location or at home, or they will be mailed a urine drug screen to use at home. Once the specimen has been provided in the test cup, the participant will either return the bag to the research staff member for immediate testing or schedule an appointment with research staff using a video chat platform (BlueJeans, Skype for Business, or Zoom through the University of Michigan) to use the urine drug screen off camera and immediately share the results with research staff. A final option is for participants to send a picture of the results to the secure study email. Research staff will record test results. After testing is complete, the urine sample will be discarded by flushing it down the toilet if done in person. No identifying information will be marked on the testing container. The validity of self-report of cannabis use and other illicit drug use may be increased when a urine drug screen is performed. Specimens will be collected in a specimen container about 4 oz. in size, although only a minimal amount of urine is needed.

Assessment Instruments	Screening/ Eligibility	Baseline	Before and/or after session	Follow Up ~8 weeks	Follow Up ~16 weeks
Demographics	X				
Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)	X				
Fagerstrom Test (for nicotine dependence)	X				
Fagerstrom Test (for cannabis dependence)	X				
Cannabis Use Disorder Identification Test (CUDIT)	X			X	X
Perceived Relief (PR)	X			X	X
STOP-BANG (Obstructive Sleep Apnea measure)	X				
Restless Leg Syndrome Questionnaire (RLSQ)	X				
Insomnia Severity Index (ISI)	X			X	X
Morningness/Eveningness Questionnaire		X			

Urine Drug Screen	X			X	X
Personal Health Questionnaire Depression Scale (PHQ-8)		X		X	X
12-Item Short Form Health Survey (SF-12)		X		X	X
Timeline Follow Back		X		X	X
Modified Self Efficacy Scale (SES)		X		X	X
Dysfunctional Beliefs About Sleep (DBAS-16)		X		X	X
Substance Use Sleep Scale (SUSS)		X		X	X
Modified Marijuana Motives Questionnaire (MMQ)		X			
Medical Marijuana Use		X			
Prescription Misuse (BOYD)		X		X	X
Side Effect Checklist (SECL)		X		X	X
Marijuana withdrawal checklist revised (MWC-R)		X		X	X
PEG Three-item Scale Assessing Pain Intensity and Interference		X		X	X
BRFSS Model 16(Marijuana Use Type)		X		X	X
Multidimensional Fatigue Inventory (MFI-20)		X		X	X
Epworth Sleepiness Scale		X		X	X
Therapy Evaluation Questionnaire		X		X	
Working Alliance Inventory-SR				X	
Daily Sleep/Wake Diary		X	X	X	X
Actigraphy		X		X	X
Session Attendance			X	X	

Primary outcomes: The ultimate goal is to use this pilot study to provide all of the necessary elements to conduct a future fully-powered RCT comparing these two conditions. We hope to assess the acceptability and feasibility of RCT procedures to determine the distribution and variability of the primary outcomes (insomnia

severity). This will be measured by the change from baseline Insomnia Severity Index score to the score at study completion.

All remuneration for the study will be in the form of gift cards or cash. Participants will be remunerated with a $40 for the completion of baseline assessment, $40 for completion of each follow-up assessment, $20 for completing four out of seven days of the daily online survey for every week before the first follow up and $10 for completing four out of seven days of the daily online survey for the week before the 2nd follow up, plus an additional $10 incentive for a urine drug screen at both follow ups. Participants will also receive $30 to compensate them for any potential charges related to the use of their technology. Participants who do not complete all therapy sessions will still receive the $30 to cover technology costs, however, they must have completed at least one phone session.

Informed consent. A two-level consent procedure will be used in this study. At screening and baseline, participants will be asked to provide informed consent. After screening, those eligible will be asked to complete a second consent. To enhance confidentiality and minimize the collection of identifying information about individuals who do not participate in the study, screening consent will be administered online (a waiver of documentation of informed consent for screening is requested) or on study provided tablet computers as the first page of the screening survey. Prospective participants that use the online screening process will enter the survey portal from a link provided in the recruitment ad (paper or electronic) directing them to the UMHealthResearch.org site, where a link for the survey will be available. After clicking the survey link, they will then be asked to review and sign an e-consent to the short screening survey. During initiation of the screening survey each participant will be assigned a unique respondent ID number by REDCap. Participants will give consent by checking a box on the electronic consent form and will self-administer a screening survey. In the event of technological issues with study tablets or internet service, or participant preference, verbal consent may be obtained for screening and paper/pencil surveys completed. Following determination of eligibility, negative screens will receive a thank you page asking for a phone number or email address to be sent their gift card and ending their participation. The only identifying information collected from those who complete the screen and are ineligible or choose not to participate in the study will be an email address or phone number, to text or email Amazon gift card codes for screening assessment remuneration. Eligible participants will be asked to provide their name, email address, and phone number for scheduling purposes. Study staff will reach out to eligible participants to schedule the urine drug screen and baseline assessment.

For those eligible based on screening responses and interested in participating in the full study, written or verbal informed consent for the full study will be obtained. Individuals interested in participating in the study will review the consent that will be emailed, texted or handed to them with the research staff in person or via a video chat platform (BlueJeans, Skype for Business, or Zoom through the University of Michigan). All participants will be told that participation is voluntary, that they can withdraw at any time, and that this will not impact any aspect of the services they receive at the clinics or dispensaries, including their ability to receive cannabis (if recruited from dispensaries). After reviewing the consent form, research staff will ask the patient if he/she has any questions regarding their participation or the study requirements and limitations. The limits of the Certificate of Confidentiality are explained in the consent form, but study staff will also verbally explain the limits of confidentiality. Any patients who request more time to review the consent form or consult with others will have the opportunity to do so. These patients will have the opportunity to have research staff contact them at a later time or to contact research staff themselves. Those interested in participating will be asked to consent to the research project. When providing informed consent, participants will be given, mailed or emailed a copy of the consent form to keep and the original will be filed in a confidential research file or study staff will record the date, time, and research staff conducting the consent in the secure database. Study staff will review the consent form for accuracy and completeness before beginning any study procedures. RAs will fully review the consent document, answer all questions and provide a copy of the consent document to the participant. All consent information will be filed in a confidential research database.

Study Eligibility Criteria.

Inclusion criteria. (1) age > 21 or older; (2) Insomnia Severity Index (ISI) score >10, indicative of at least "mild" insomnia; (3) use of cannabis three times a week within the past three months; (4) self-reported use of cannabis to manage insomnia at least once a week over the past month; (5) consistent access to a telephone, smartphone, laptop, or tablet; and (6) a positive urine drug screen for THC.

Exclusion criteria. (1) individuals who do not understand English; (2) individuals judged unable to provide informed consent (e.g., intoxication, mental incompetence, psychosis, bipolar disorder); (3) diagnosis or high suspicion of a sleep disorder other than insomnia based on validated self-report measures; (4) self-reported cancer; (5) self-reported pregnancy; (6) self-reported rotating or night (3rd) shift work; (7) resides a distance greater than 50 miles from Ann Arbor. Participants will not be excluded if they are taking prescription or over the counter medications for sleep, however they will need to report being stable on the medications for at least 8 weeks and agree to maintain the same regime throughout the study. Those who have been taking prescription medications for sleep for less than 8 weeks, or who report they are unable to continue with their medications for the duration of the study (approximately 16-18 weeks) will be excluded.

Research staff will use their clinical judgment to assess cognitive ability to consent. If necessary, recruitment staff may require a potential participant to pass a brief mental status exam. Potential participants may be excluded based on participant best interest (e.g., adult patient with a legal guardian; or if study staff know a patient or their family personally, in order to fully ensure participant privacy), with PI approval.

Justification for selection criteria. Participants in this study will be 21 years old and older for several reasons. First, although state law does allow individuals under the age of 18 to obtain cannabis for medical purposes with consent of a legal guardian, available data indicate that very few adolescents have been issued medical cannabis cards in Michigan. In addition, with the new recreational marijuana laws allowing non-medical use of cannabis, we are not solely recruiting medical cannabis users. This new law states all recreational marijuana uses must be 21 years or older to possess or use marijuana. Therefore, all participants should be age 21 years or older to follow Michigan recreational marijuana laws.

In order to collect interview data from a sample that will be representative of the population to be recruited for the RCT, we will exclude those with self-reported cancer or pregnancy. Individuals who use marijuana for cancer may experience a different trajectory than those who are not and women who self-report that they are pregnant will be excluded because: (a) of the potential risks of study participation to pregnant women; and (b) we are unlikely to have sufficient numbers of pregnant women to facilitate meaningful subgroup analyses.

Access to a smartphone, computer, or tablet is required to deliver intervention sessions, as all sessions are meant to be delivered remotely via BlueJeans video chat or telephone. Those who do not report having reasonable access to the technology needed for the study will be excluded.

Potential Risks, Minimizing Risks, and Potential Benefits

1. Potential Risks

a. Loss of Confidentiality

The major potential risk to study participants is violation of confidentiality of survey and interview data. The risk of violation of confidentiality exists because participants will be disclosing personal information in surveys and interviews. This risk is related to the damage that could be caused by an inadvertent release of sensitive information (e.g., substance use, medical conditions). Participants will be informed of the procedures taken to protect their confidentiality.

b. Discomfort During Interview

There is also a slight risk of psychological discomfort to study participants as a result of being asked personal questions on sensitive topics. Participants may also become anxious or upset during discussions of their thoughts about managing their insomnia or substance use during the interview.

2. Minimizing risk

a. Loss of confidentiality (risk unlikely)

To minimize the violation of confidentiality, we will ensure that data are protected and cannot be linked to a particular person. Unique identification numbers will be assigned to each participant and all forms are coded with this number, rather than by name. All data are stored in locked file cabinets. Consent forms and subject code/name sheets will be stored separately, because they contain identifying information. Data entry staff will work with forms that contain only subject numbers. Physical security of data will be assured by daily and weekly back-ups. Data cleaning will be conducted throughout the data collection period to ensure the production of a final dataset for analysis at the end of data collection.

Study data will be collected and managed using REDCap (Research Electronic Data Capture). Participants' names and contact information will be stored in a secure, REDCap database, separate from their study data and only accessible to members of the research team for research purposes. REDCap is a secure web application designed to support data capture for research studies. It provides userfriendly web-based case report forms, real-time data entry with branching logic and validation (e.g. for data types and range checks), audit trails, a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus), procedures for importing data from external sources, and advanced features such as a data quality check module. The system was developed by a multiinstitutional consortium initiated at Vanderbilt University. REDCap servers are physically located in the University of Michigan Medical School Information Systems (MSIS) data center. Application and database servers are on virtual machines (VM). The VM servers are Red Hat Enterprise Linux Server 5.6 (64-bit, 2.6.18 238 e15-smp kernel) 2x AMD Opteron 6174 5.0.95 2.2 GHz with 4 GB RAM, running Apache 2.2.3 (application servers) and MySQL (database servers). Physical security for the databases is provided in a professionally managed and equipped tier-2 data center with tightly controlled access. Remote data access employs SSL encryption and 2-tier Kerberos/Level 1 and UMHS Level 2 password challenges via LDAP authentication. Access to the application, the database, and the underlying systems infrastructure are consistent with industry best practices including HIPAA security and privacy requirements and the HITECH Act. The applicationprovides audit trails on user access to MICHR and MSIS technical and support teams. Backup of data is managed by MSIS and vulnerability testing is performed regularly by the University of Michigan Health

System Medical Center Information Technology. Risk evaluation is performed using a methodology derived from NIST Special Publication 800-53 – "Recommended Security Controls for Federal Information Systems" and is used to refine and improve operating policies and procedures. Daily backups and VM snapshots of the application and database servers are stored on a remote storage device. The restoration of the servers from a hardware or software failure are protected for 24 hours of disaster recovery.

To test a new participant tracking program, participant personal information will also be kept in Ripple™, a secure web application designed for the storing and management of personally identifying information of research participants. Ripple was initially developed at the University of Michigan to provide a user-friendly, web-based secure interface where research teams can centralize the storage and management of research participants' personal information, including name, participant ID, demographics, and study workflow (e.g., appointments). Participant information managed with ripple is private and secure. This information is kept in

fully encrypted format inside dedicated databases that are segregated from other Ripple accounts and thus only authorized study staff will have access to the study data. Likewise, Ripple infrastructure complies with the privacy and security guidelines of the Health Insurance Portability and Accountability Act (HIPAA), including 2048-bit data encryption in transit and at rest, automatic logoff, audit trail, daily backups in triplicate dedicated servers, firewall, custom access permission for lab members, zxcvbn password strength estimation, and enterprise administrative safeguards to prevent unauthorized staff from accessing participant information. Furthermore, Ripple is used only for storing personally identifiable information of participants and is not used to capture other research data (e.g., questionnaires, health records, etc.). This ensures that the personally identifiable information and research data are segregated. As this is a pilot program, Rippple is only available to us for approximately 6 months of use. To avoid any data loss, participant tracking information will also be kept in REDCap, as mentioned above and as previously done in the beta testing phase of this project.

Interviews will be audio-recorded with participant permission for fidelity and may take place in person, via an online video chat (BlueJeans), or over the phone. The intervention sessions may be remotely delivered via telephone or BlueJeans video conferencing (https://www.bluejeans.com/). BlueJeans provides a cloud-based audio/video/content-sharing conferencing service. The service is vendor-agnostic and allows up to 150 endpoints to connect for a meeting. U-M's current contract with BlueJeans enables all U-M faculty, staff, and students to register for a BlueJeans User Account. BlueJeans collects and maintains data related to the date, time, and attendees of a meeting. Actual video or audio content is only stored by BlueJeans when the meeting host turns on the recording feature. We will not be using the recording feature on Bluejeans. U-M's agreement with BlueJeans includes a Business Associate Agreement. This means individuals may use this service to share Protected Health Information (PHI) regulated by HIPAA. For more information, BlueJeans Security and Privacy agreements with the University of Michigan can be found at https://safecomputing.umich.edu/dataguide/?q=node/181. The audio recordings for the interviews will be done with a digital voice recorder. The audio-recordings of the interviews will be destroyed after the files are uploaded to a password-protected, secure server with restricted access. Participants will be asked not to mention names or other identifying information in during the recorded interview. Due to an increase in use in the BlueJeans platform during the COVID-19 pandemic, we are also including the ability for research staff to use alternate video platforms approved by the University of Michigan, including Skype for Business, or Zoom through the University of Michigan.

We have set up an email account to be used for subjects to contact study staff or for study staff to send appointment reminders and online surveys (via REDCap) to subjects. The e-mail address is: UM-CannSleep@med.umich.edu.

b) Discomfort during assessments (risk likely):

Participants may become upset, anxious, or uncomfortable as a result of being asked very personal questions. To minimize this risk, all interviews will be conducted in private offices with skilled research staff. Research assistants will be trained to respond to this emotional distress and to refer participants to appropriate resources as necessary. Specifically, this training will include information regarding evaluating warning signs of distress that could occur as a result of the screening, intervention, or assessments, and means of addressing such issues and minimizing distress. Such strategies will include maintaining an empathic response, acknowledging the distress through reflection, avoiding blame, processing in a non-blaming non-confrontational manner, and eliciting or encouraging use of relaxation and cognitive calming strategies. Crisis procedures, effective in previous projects conducted by the study investigators, will also be utilized, including immediately paging Drs. Ilgen or Arnedt (Multiple PIs) for consultation. If any research staff observes any indication of potential distress, including through review of responses to the assessments, further evaluation of the participant will be conducted by a licensed clinician. All participants are free to terminate the interview at any time or refuse to respond to any question. As with any research project, unexpected events are always possible. If risk is

determined to be present, we will implement our standard clinical protocol for responding to suicide risk, including giving participants a resource brochure. Ongoing follow-up will occur until it is determined that risk is minimal.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

It is believed that research participants may be helped by participating in this study. Participants who receive the CBTi-CB intervention will receive a therapeutic intervention aimed to improve their insomnia symptoms and related functioning during the day. CBT for insomnia has known risks associated with its use, but these are usually tolerable and subjects may not otherwise receive treatment for insomnia. Thus, the risks associated with participating are reasonable in light of the potential benefits to the participating subjects and others. The information control condition represents an increased (enhanced) level of care from standard medical cannabis treatment provided at clinics.

4. Importance of the Knowledge to be Gained

The risks to subjects associated with participating are reasonable compared to the potential knowledge to be gained. Identifying an effective and safe non-medication treatment for insomnia, a highly common co-occurring condition this population of individuals seeking cannabis, could improve nighttime and daytime symptoms and reduce cannabis use. Our study would be the first to evaluate a highly effective sleep-focused intervention and determine the effects on cannabis use in a non-treatment seeking population.

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