MINIMAL RISK CLINICAL RESEARCH PLAN cphs v. 9/19/2019

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1. Introduction and Background

The majority of opioid users meet criteria for anxiety and depressive disorders (Applebaum et al., 2010). However, many substance use disorder treatment programs do not offer treatment for co-occurring mental health problems (Watkins et al., 2004). The role of anxiety and depression also appears to be directly linked to opioid use itself. For instance, experimental research has shown that craving for opioids can be induced by depressed and anxious mood manipulations, suggesting a potential causal role between momentary anxious and depressed affect and daily craving among opioid users (Childress et al., 1994; Hogarth et al., 2019). Anxiety and depressive disorders also increase the likelihood of overdose among persons with OUD (OUD; Bartoli et al., 2014). Among persons who receive treatment for OUD, depression also predicts an increased risk of relapse (Kosten, Rounsaville, & Kleber, 1986).

Consequently, treatments have been developed for anxiety and depressive symptoms for opioid users (Hassan, Howe, Samokhvalov, Le Foll, & George, 2017; Pani, Vacca, Trogu, Amato, & Davoli, 2010). A meta-analysis of the literature suggests that the efficacy of psychotherapy on treating anxiety and depressive disorders in persons receiving opioid agonist treatment has shown more beneficial effects than pharmacotherapy interventions designed to treat anxiety and depressive symptoms among the same population (Hassan et al., 2017). These interventions have been primarily based on cognitive-behavioral therapy, including behavioral and relaxation-based strategies. Nevertheless, few treatment facilities offer these in-person interventions due to their high cost and time burden. More importantly, clinicians in addiction treatment programs are not trained in the treatment of mental health, and, consequently, the implementation of these interventions would require hiring new personnel. However, studies have consistently shown strong intervention effects for anxiety and depression using app-based digital interventions among those with primary anxiety and depressive disorders (Firth, Torous, Nicholas, Carney, Pratap, et al., 2017; Firth, Torous, Nicholas, Carney, Rosenbaum, et al., 2017). These app-based interventions can decrease barriers to access, including the need to obtain childcare in order to participate in treatment, stigma, and cost (Wilhelm et al., 2019).

To our knowledge, no studies have examined treatment for anxiety and depression among those receiving treatment for OUD to determine whether (a) receiving anxiety and depressive treatment can be used to augment care via low-cost and scalable technology-based digital interventions, or, (b) by reducing anxiety and depressive symptoms, there would be a corresponding reduction in craving or opioid use behaviors among those receiving care for OUD. Given the deficits in research on treatments for anxiety and depression among those with OUD, the current research will examine the efficacy of a digital intervention designed to treat anxiety and depressive symptoms by augmenting the state of the science medication-based OUD treatment.

This work could lead to a low-cost scalable solution to augment gold-standard treatment as usual in OUD by decreasing levels of comorbidity of anxiety and depressive disorders, thereby ultimately improving the

outcomes of OUD itself. If successful, this work will directly translate into a future R21 proposal, delivering low-cost technology-based interventions to a larger cohort of OUD patients.

There is also a need to personalize these treatments. Personalized assessments of depressive and anxiety symptoms can be studied by studying individuals intensively across time and creating models of each individual's behavior.[19] This approach is primarily based on the ergodic theorem (i.e., a branch of mathematics regarding the study of dynamical systems, and the mathematical conditions required to measure the dynamic process of within-person changes)[20] and regards the conditions required for group-based data to apply to individual behavior.[21] In contrast to subtyping approaches to anxiety and depression that capitalize on analyzing between-person variance, these personalized approaches capitalize on within-person variance by studying individuals intensively across time.[24] This work constitutes a large step towards the development of precision medicine of anxiety and depression, aligning with both White House calls for precision medicine, the National Institute of Mental (NIMH)'s inclusion of personalization as a central part of their strategic plan, and the calls for personalization research in top outlets, such as *Science*, *Nature*, the *Lancet*, and the *Journal of the American Medical Association*.[25–30] Although this approach has been shown to be directly capable of personalizing interventions,[31,32] results to date have solely relied on self-report measures of anxiety and depressive symptoms. This research highlights the *need to develop objective, personalized assessments of anxiety and depression by utilizing intensive, longitudinal data*.

Most of these studies focused on predicting changes in depression and anxiety symptoms across weeks (i.e., long-term within this context). The majority of these studies also utilized unselected samples, rather than analogue (i.e., persons reporting high depressive symptoms, but not assessed for diagnostic criteria) or diagnostic samples (i.e., persons diagnosed with The work on unselected samples suggested that smartphone-based location data could be used to predict symptom changes across 10-week intervals (rs 0.4–0.5)[50] and held weak and inconsistent relationships between symptoms 3 to 6 weeks later (rs between 0.0–0.2).[51] In another unselected sample, smartphone usage data was associated with symptoms across 7 to 14 days (rs 0.0–0.4).[52] In other unselected samples using multiple sources of data, smartphone data were able to differentiate persons who are high or low in depressive symptoms across 2-week intervals by utilizing movement, location, and usage patterns (59–60% accuracy).[53] Another study, using an unselected sample, suggested that approximately half of the variance in change in symptoms across weeks could be explained by movement, heart rate, sleep duration, and location when combining smartphone and wearable devices ($R^2 = 0.44$).[54] Several studies have predicted changes in depressive symptoms using smartphones among persons with bipolar disorders and have shown that depressive symptom changes can be predicted from smartphone use, movement, social contact, and location across 9 days to 8 weeks.[55–60] Only two studies have examined change in : (1) one of these studies only included six people and found large differences across persons in analyzing smartphone data;[61] and (2) our study with 55 participants showed that changes ins using wearable psychomotor retardation and sleep data, alone ($r = 0.8$).[48] Thus, in examining changes in across weeks, few studies have examined persons , and *the results suggest that large person-specific differences exist, and a large variety of passive sensing data may capable of accurately predicting changes symptoms, perhaps even that a combination of these symptoms may hold even greater utility than one stream alone.* However, by design these models also not capture heterogeneity experiences.

We will also be collecting passive sensing data to potentially see if these interventions can be personally tailored to individual needs based on the passive sensing data.

A. SIGNIFICANCE

Urgent Need to Address Anxiety and Depression Comorbidity among Persons with OUD. Anxiety and depressive disorders frequently co-occur among persons with OUD. Moreover, research suggests that the presence of anxiety and depressive disorders among those with OUD are linked to a threefold risk of suicide attempts (Maloney, Degenhardt, Darke, & Nelson, 2009), compared to those with OUD alone. Among persons who receive treatment for OUD, depression also predicts an increased risk of relapse (Kosten et al., 1986). However, persons with OUD rarely seek treatment for anxiety or depressive disorders and often do not believe that they need treatment for either disorder despite meeting diagnostic criteria (Stein, Santiago Rivera, Anderson, & Bailey, 2017). Moreover, few substance use disorder treatment programs offer treatment for these co-occurring mental health problems (Watkins et al., 2004).

Potential Role of Anxiety and Depression in Influencing Opioid Use Behaviors. From a behavioral perspective, negative reinforcement of internal negative aversive states appears to be a strong driver of opioid use among persons with OUD (Blume, Schmaling, & Marlatt, 2000). This is exemplified by research examining the potential causal relationship between anxiety and depressive mood states and cravings among persons with OUD. For example, one study recruited 10 persons with OUD who had been abstinent for 30 days and randomized participants to either watch a depressive scene or be guided through self-hypnosis and found that opiate cravings increased from pre to post induction after the depressive scene exposure (Childress et al., 1994). Among persons receiving medication therapy for OUD (N = 14), another study found that an anxiety manipulation increased cravings from baseline, but a neutral manipulation condition had no significant effect on cravings (Hyman, Fox, Hong, Doebrick, & Sinha, 2007). Among 66 persons with OUD receiving medication treatment, participants who felt increased sadness in response to a video clip experienced increased cravings from pre to post, and this effect was moderated by anxiety (Stathopoulou, Pollack, & Otto, 2018). Lastly, another study showed that negative mood state manipulations were a trigger for heroin-seeking among persons with OUD (Hogarth et al., 2019). Taken together, these findings suggest that anxiety and depressive moods play a potential causal role in cravings and opioid use among persons with OUD.

Treatment of Anxiety and Depressive Symptoms among Persons with OUD. Based on these strong relationships, treatments have increasingly been developed to treat anxiety and depressive symptoms among persons with OUD (Hassan et al., 2017; Pani et al., 2010). A meta-analysis of the literature suggests that the efficacy of psychotherapy on treating anxiety and depressive disorders in persons receiving opioid agonist treatment have shown more beneficial effects than pharmacotherapy interventions designed to treat anxiety and depressive symptoms among the same population (Hassan et al., 2017). Nevertheless, there are several barriers to implementing these interventions within the opioid patient population at large. For instance, these interventions typically required 8-24 sessions with an in-person mental health treatment provider (Hassan et al., 2017), which often creates barriers to care due to lack of access and cost (Wilhelm et al., 2019). Notably, technology-based treatments offering cognitive-behavioral therapy may be delivered at limited cost. A large literature has shown that app-based digital interventions produce strong effects in treating anxiety and depression (Firth, Torous, Nicholas, Carney, Pratap, et al., 2017; Firth, Torous, Nicholas, Carney, Rosenbaum, et al., 2017). Although treatments have been developed to treat depression among persons with other substance use disorders (e.g., alcohol and marijuana; Cunningham et al., 2018; Deady, Mills, Teesson, & Kay-Lambkin, 2016; Kay-Lambkin, Baker, Lewin, & Carr, 2009), no studies have evaluated the use of digital interventions in treating anxiety and depressive symptoms among persons with OUD.

Expected Impact in Reducing Comorbidity among Persons with OUD. As most substance use treatment facilities are unable to address anxiety and depressive disorders and the treatments that are available to address anxiety and depressive disorders among persons with opioid disorders are not broadly disseminated, the creation of a low-cost, scalable treatment to address anxiety and depressive disorders within this population could have an impact on the total distress and functional impairment caused by anxiety and depression. There is reason to suspect that uptake of these interventions will be substantial given that: (1) patients in medication-treatment for OUD are highly willing to participate in stress-reduction treatments and (2) high anxiety levels are associated with a greater willingness to participate in treatment (Barry et al., 2011). As importantly, given the causal nature of anxiety and depression on cravings and opioid-seeking behaviors, effective treatment of anxiety and depressive symptoms may also result in decreased cravings and opioid use behaviors among persons receiving treatment. Thus, the development of an efficacious technology-based intervention could provide scalable stepped-care to a vulnerable population and also enhance outcomes for OUD.

B. INNOVATION

The widespread high comorbidity and untreated anxiety and depressive disorders among persons receiving treatment for OUD highlights the need for the development of new scalable treatments for anxiety and depressive symptoms within this population. Thus, the overarching innovation of this study is evaluating a scalable intervention treating anxiety and depressive symptoms among persons receiving treatment for OUD. This intervention involves a brief video from our PI explaining differing relaxation and mood control techniques as well as the science behind these. Please see attached for an example: https://www.dropbox.com/s/o8ncxhlnvp8y1u2/Exercise_Intervention_Video_Example.mov?dl=0 . We will be covering techniques such as improving physical activity, muscle relaxation, nutrition and more. This study has the potential to reduce anxiety and depressive symptoms, increase the efficacy of medication treatment for OUD, and potentially decrease the long-term relapse rates and deleterious outcomes (i.e., given that anxiety and depressive disorders are associated with an increased risk of relapse). Specific innovations include:

1. Developing a novel technology-based intervention for anxiety and depressive symptoms among those receiving medication treatment for OUD.
2. Evaluating the feasibility of a technology-based intervention for anxiety and depressive symptoms among persons receiving treatment for OUD.
3. Evaluating the efficacy of a technology-based intervention for anxiety and depressive symptoms among persons with OUD.
4. Evaluating the efficacy of a technology-based intervention treating anxiety and depressive symptoms on cravings and opioid use among persons receiving medication treatment for OUD.

2. Objectives and Hypotheses

Aim 1: To test the feasibility and acceptability of the digital intervention designed to treat anxiety and depressive symptoms among persons receiving medication treatments for OUD.

Hypothesis 1: The digital intervention will show feasibility based on the ability to recruit participants (N = 40 within the digital intervention + medication treatment, N = 40 with medication treatment) and demonstrate acceptability of the application with greater than 50% of the intervention sessions completed on average by the treatment group.

Aim 2: To test the efficacy of a digital intervention targeting anxiety and depressive symptoms among persons receiving medication treatment for OUD. Sixty participants receiving medication treatment for OUD will be randomized to receive a digital intervention to treat anxiety and depression (N = 30) or care as usual (N = 30) for a total of four weeks.

Hypothesis 2: The digital intervention app group will experience (a) greater symptom reduction in anxiety and depressive symptoms (based on self-report measures) and (b) decreased opioid cravings and use across a four-week period (based on self-report measures and urine tests).

3. Study Design

Describe all study procedures, materials, and methods of data collection:

Recruitment. A population of 3000 adults who are receiving medication treatment for OUD will be recruited from an online study based on Google Adwords and Facebook advertisements as online recruitment has been shown to be a viable and cost-effective recruitment method for opioid users (Marshall et al., 2018).

We would also like to expand our recruitment efforts to Reddit sub-pages as well. Previous researchers looking at opioid addiction have had success posting in the Reddit forums and we would like to also recruit using this platform.

Inclusion Criteria. (a) Adults (age 18 or older), (b) fluent in English, (c) able to provide informed consent, (d) meet current criteria for OUD (as defined by a Rapid Opioid Dependence Screen), (e) are receiving methadone, buprenorphine, and/or naltrexone for OUD, and (f) meet current criteria for an anxiety and/or depressive disorder (based on the Patient Health Questionnaire and the Generalized Anxiety Disorder Questionnaire).

Procedure.

Screening: Participants will complete the Initial Consent form, giving the study team permission to collect survey answers to the PHQ-9, GAD, Opioid Craving Scale, and RODS as well as contact information. If eligible the participants will move on to the main consent form stage.

Main Study: Participants will complete the main consent form. Participants will complete self-report assessments on their anxiety symptoms, depressive symptoms, opioid cravings, and opioid use behaviors. Participants will be randomized to a smartphone-based digital intervention or waitlist control condition. The control group can receive the intervention once they have completed the one-month follow up section of the study if they would like it. The digital intervention will be designed to treat participants' anxiety and depressive symptoms, and participants will be asked to use the intervention four times per week for four weeks (16 digital sessions). Participants will complete post measures and one-month follow-up measures on anxiety symptoms, depressive symptoms, opioid cravings, and opioid use behaviors. The Precision Dx12-panel test cups (manufactured by American Screening Complete Drug Test Solutions) will be mailed to participants. Participants will also be asked to complete five urine tests to detect substance use (amphetamines, barbiturates, benzodiazepines, cocaine, ecstasy, marijuana, methamphetamine, opioids, oxycodone, and propoxyphene) across the study (1 at pre-digital intervention, 1 during the digital intervention, 1 post-digital intervention, 1 between post and follow-up of the digital intervention, and 1 at the 1-month follow-up of the digital intervention). Participants will be instructed when to complete each urine test and will be asked to take a photo of the back the label of each test showing the results to the experimenters and to text these photos to a Google Voice Number maintained by the experimenters. Both the digital intervention group and the control group will receive the same follow-up assessments and be asked for the urine samples. Following the study, the control group will be able to access the intervention and have access to the study team for support.

The Link for the intervention videos is below:

https://drive.google.com/drive/folders/1aGv-d85VnuriTcta9dkRt6OjizcMHrF2?usp=sharing

4. Analysis

Describe any qualitative tests and measures as well as quantitative methods:

Measures. **Rapid Opioid Dependence Screen (RODS; Wickersham, Azar, Cannon, Altice, & Springer, 2015).** The RODS will be utilized to screen persons for OUD. The RODS is an eight-item questionnaire inquiring about tolerance; withdrawal; unintended dosage or duration of use; persistent desire and unsuccessful quit attempts; time spent obtaining using and recovering from opioid use; missing important social, occupational, or recreational activities due to opioid use; and continued use despite adverse consequences. The RODS has demonstrated strong interrater agreement with diagnostic interviews (kappa = 0.67, sensitivity = 0.97, specificity = 0.76; Wickersham et al., 2015).

Current OUD Treatment. Participants will be asked whether they are (1) receiving treatment for OUD and (2a) prescribed methadone, (2b) prescribed buprenorphine, and/or (2c) prescribed naltrexone. To qualify for the present study, participants must report receiving treatment for OUD and being prescribed methadone, buprenorphine, and/or naltrexone.

Opioid Craving Scale (McHugh et al., 2014). The Opioid Craving Scale measures opioid cravings using three questions: (1) "How much do you currently crave opiates" (0 *Not at all* – 10 *Extremely*); (2) "In the past week, please rate how strong your desire to use opiates has been when something in the environment reminded you of opiates" (0 *No desire* – 10 *Extremely strong Desire*), and (3) "Please imagine yourself in the environment in which you previously used opiates. If you were in the environment today and if you were the time of day that you typically used opiates, what is the likelihood that you would use opiates today?" (*Not at all* 0 – 10 *I'm sure I would use opiates*). This brief instrument has been shown to predict opioid use in the subsequent week, with a 1 unit increase on this 10-point scale being associated with a 17% higher increase in the likelihood of engaging in opioid use behaviors (McHugh et al., 2014).

Generalized Anxiety Disorder Questionnaire – IV (GAD-Q-IV; Newman et al., 2002). The GAD-Q-IV will be used to assess DSM-5 generalized anxiety disorder. The GAD-Q-IV demonstrated good sensitivity (89%) and specificity (82%) in diagnosing generalized anxiety disorder compared to diagnostic interviews (Moore, Anderson, Barnes, Haigh, & Fresco, 2014). Although originally designed to measure the DSM-IV criteria, the DSM-5 criteria for generalized anxiety disorder has remained the same; thus, this measure assesses both DSM-IV and DSM-5 generalized anxiety disorder.
Difficulties in Emotion Regulation Scale (DERS)(Gratz, K. L. & Roemer, L. (2004) The DERS will be used to measure difficulties in emotion regulation. It contains 36 items using a 5 point Likert scale.

CTBH self-regulation scale: Our findings provide a 12-item momentary self-regulation scale that can capture self-regulatory dynamics at a momentary level. The SOBC scale is in a table at the end of the document- response options are 1-5; 1 = "not at all" and 5 = "extremely".

Passive Sensing Data: The app will continuously collect passive sensing data on patterns in 1) sleep duration and quality;(2) light (3) location; (4) movement (5) social contact including duration and frequency of incoming and outcoming calls and text messages; (6) screen time; and (7) heart rate variability; (8) sound levels captured through passively collected smartphone.

Patient Health Questionnaire-9 (PHQ; Kurt Kroenke & Spitzer, 2002). The PHQ will be used measure symptoms of major depressive disorder. The PHQ is the most widely utilized instrument to measure major depressive disorder (Walker et al., 2018). The PHQ is based on based on nine self-report Likert scale items. The patient health questionnaire has demonstrated high sensitivity (77–88%) and specificity (88–94%) in measuring major depressive disorder (K. Kroenke, Spitzer, & Williams, 2001).

Technology-Based Digital Intervention. The digital intervention will be a prototype, and the current trial will be used to continue to both develop and refine the intervention. The current intervention will be based on a combination of cognitive-behavioral principles. As with prior research, the mobile platform will be delivered via Qualtrics, a HIPAA compliant and mobile-friendly platform (Levin, Navarro, Cruz, & Haeger, 2019). The cognitive-behavioral therapy will be primarily based on components with strongest support in digital interventions (Kenardy et al., 2003; Krupnick et al., 2017; Lange et al., 2003). The platform will deliver interactive interventions where participants will view texts and images, and it will also allow user interaction. **Diaphragmatic Breathing and Progressive Muscle Relaxation (four virtual sessions).** A brief diaphragmatic breathing and progressive muscle relaxation protocol will be the first four sessions of treatment as these interventions are effective in treating generalized anxiety disorder (Borkovec, Newman, Pincus, & Lytle, 2002). **Activity Planning and Behavioral Activation (four virtual sessions).** Activity planning and behavioral activations will be designed to include pursuit of both pleasurable and goal-directed behavior. Given the strong literature surrounding exercise as a discrete intervention component of behavioral activation reducing anxiety and depressive symptoms, participants will be asked to set their own exercise goals. **Writing Exposures (four virtual sessions)**. Based on a previous internet-based protocol, we will integrate writing exposures to treat participants' most significant fears (note that fears naturally occur in nearly all persons in the population even if the participant is not above clinical levels of anxiety). First, we will include a brief rationale for engaging in exposure therapy. Participants will then be asked to write about the nature of fears in detail, describing intimate fears and thoughts, writing in the first person and in present tense, relating olfactory, visual, and auditory sensations. The goal of this work is to provide a transdiagnostic ability to treat a variety of fears (e.g., this could target fears related to trauma, social anxiety, or interoceptive fears). **Cognitive-Reappraisal (four virtual sessions).** Participants will be educated about common principals of cognitive reappraisal in order to instill new insights. Participants will be asked to include positive aspects of trauma and aversive

experiences on their lives. Participants will also be asked to restructure their own thoughts. The platform will send reminder texts and emails when it is time to complete the new session. Additionally, the platform will also send targeted texts and emails to users who have not completed the intervention two days later and send a third text message and email asking if they were having any difficulty in accessing the intervention if they have not completed the intervention within three days after the scheduled time. **Qualitative Feedback.** In order to further refine the digital intervention, qualitative feedback on the digital intervention will also be solicited. This will include the participant's level of satisfaction with the intervention, perceived benefits, and recommended modifications, combining both Likert and open-ended feedback. **Refinement.** Following the conclusion of the study, the qualitative feedback and usage patterns will be used to further refine the intervention.

Analyses. To test feasibility for ***Hypothesis 1***, we will determine whether we can achieve the targeted enrollment (N = 80) and whether the average number of digital sessions is significantly higher than 50% based on multilevel binomial test nesting individual session completion rates within persons. To test **Hypothesis 2**, the current proposal will use intent-to-treat analyses employing multilevel modeling to examine moderation of change across time from pre to post, and post to follow-up. Based on power analyses, we will be well-powered to test the effects of the intervention (3-5 data points per person x 80 participants = 180-300 x 80% adherence = 144-240 data points total).

5. Study Progress Monitoring

Note: appropriate monitoring may include periodic assessment of the following:

- data quality
- timelines
- recruitment and enrollment

Provide a description of the methods which will be used to determine the progress of the study, including periodic assessments of data quality, timelines, recruitment, and enrollment as appropriate:

Recruitment. A population of 3000 adults who are receiving medication treatment for OUD will be recruited from an online study based on Google Adwords advertisements as online recruitment has been shown to be a viable and cost-effective recruitment method for opioid users (Marshall et al., 2018). We are only recruiting from the US.

We will also recruit via Reddit forum as well. Please see the document with the example of the post we would be planning on using.
Six opioid-focused subreddits were initially identified. Subreddits were selected based on their topical focus and their popularity. All were devoted to discussion of opioid use or recovery. In September 2019, the number of Redditors subscribed to each subreddit ranged from 4,000 to 82,000 people. Each subreddit was monitored by multiple moderators, who ensured all posts follow the Reddit community guidelines and remain focused on the topic of interest. All moderators in each of the six subreddits will be contacted by the study team to obtain approval to post the survey description and hyperlink. Moderators will be sent a study information sheet and a link to view the study description.

Once the moderators provided approval, a description of the study and the Qualtrics link will be posted in each subreddit. This post described the study purpose, the survey, A moderator will then marked each post as "Moderator Approved", which will pin the post near the top of each subreddit, increasing the post's visibility. Any Redditor who viewed the post could then click on the survey hyperlink and be taken to the survey informed consent page in Qualtrics. Redditors could also post comments or links in response to the survey posts. These comments were monitored by the research team for the duration of recruitment. The research team responded within 12 hours to any questions posted about the study.

We expect dropout to be high (if they are ineligible due to the screening process).

Inclusion Criteria. (a) Adults (age 18 or older), (b) fluent in English, (c) able to provide informed consent, (d) meet current criteria for OUD (as defined by a Rapid Opioid Dependence Screen), (e) are receiving methadone, buprenorphine, and/or naltrexone for OUD, and (f) meet current criteria for an anxiety and/or depressive disorder (based on the Patient Health Questionnaire and the Generalized Anxiety Disorder Questionnaire). We are currently trying to get the app to work with both IOS and Android phones. If the app is not compatible with IOS, we may have to limit our sample to Android Users.

6. Risks & Benefits

Note: Risks may be physical, psychological, social, legal, economic, to reputation, or others.

a. Describe any potential risks, their likelihood and seriousness:

c. Potential Risks

There are no high risks or hazardous aspects of the proposed study. Nevertheless, we realize that interventions and assessments may promote increased focus on their mental health symptoms, compared to before they started the study. Research suggests that assessments are associated with *decreases* in MDD symptoms (Bakker & Rickard, 2018; Kauer et al., 2012). To date, the principal investigator has collected data from over 10,000 participants asking them to engage in anxiety and depressive interventions and experienced no known adverse events (Jacobson & Wilhelm, 2019). Given this, although there is a possibility that a subset of persons could react negatively to the intervention, it is also very unlikely to occur. Additionally, referrals for in-person treatment will be offered in the event of worsening suicidality or at the request of participants (see **Clinical Referrals** *below*). If any participant appears to be in crisis, appropriate action will be taken based on established suicide and crisis assessment protocols. Participants who report concerning levels of symptoms will be highlighted via algorithms as requiring contact and in-person referrals.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

Recruitment. Recruitment will take place via Google Adwords and Reddit. **Informed consent.** The informed consent prior to the screen will provide information about the nature of the study in its entirety, including both information about the questions asked during the screen, data storage and retention plan, who will have access to this information, and responses to any participant questions. Participants will also be informed of the potential risks, benefits, and measures taken to protect participant confidentiality, and they will be provided an opportunity to ask questions about the study.

b. Protection against Risk

Protection of Privacy. Participants' privacy will be safeguarded by fully informed consent by informing participants what data will be collected, who will have access to this information, and how knowledge of how information collected will be utilized and disseminated (Ziegeldorf, García-Morchón, & Wehrle, 2014).

Exclusion of High-Risk Populations. The current study will exclude persons who will be at high risk, specifically those with: (1) active suicidality, (2) psychosis, and (3) bipolar disorder. Treatment referrals will be made to those persons (see **Clinical Referrals** *below*).

Clinical Expertise. All research will be overseen by Dr. Jacobson who has a doctorate in clinical psychology.

Availability of the Study Team. Dr. Jacobson will be available to discuss the study or any concerns about the study with participants if requested by the participant. Dr. Jacobson will be available in the event of a clinical emergency, and this availability will be clearly communicated orally and in writing to study participants. Participants will be provided information such as how to reach the investigators in the event of a clinical emergency. Participants will be referred to a treatment resource or a higher level of care if needed (i.e., hospitalization). Participants will be referred to a higher level of care if there is evidence of (1) acute active suicidality with a plan and intent to take one's life within a delineated period of time (i.e. less than 1 year), (2) acute homicidally with a plan or intent to take another's life, or (3) likelihood that they could immediately cause severe bodily harm to themselves or others (see **Clinical Referrals** *below*).

Ability to Withdraw. Participants may be able to withdraw from the study due to a significantly deteriorating course (e.g., need for hospitalization) or if the PI or participant determines that staying in the study is not in the participant's best interest. All participants who withdraw will be provided referrals for treatment.

Clinical Referrals. All participants will be given the phone number for the National Suicide Prevention Hotline, which is funded by the Substance Abuse and Mental Health Services Administration (SAMHSA). The hotline is staffed 24/7 by licensed mental health providers and is available throughout the United States. For persons not in acute risk who need a referral to outpatient treatment, we will identify referral sources using the Anxiety and Depression Association of America (ADAA), the Association for Behavioral and Cognitive Therapies (ABCT), the American Psychiatric Association, and the American Psychological Association. Each of these organizations maintains an active registry of current psychologists and psychiatrists across the country, many of whom provide the ability to also specify persons specializing in treating anxiety and depression.

, the study team believes that referring participants to helpful resources is sufficient given the nature of the study. We will not be actively monitoring suicidality throughout the study and will only ask the PHQ-9 at certain points during the study. If participants give concerning responses when questionnaires are administered there will be an automated referral process to initiate resources if persons indicate high suicidal ideation.

Additionally, there is evidence that administering questionnaires such as the PHQ-9 do not increase an individual's likelihood of suicidality. We do not believe that our study questionnaires will increase this likelihood. Again, anyone indicating suicidality in the screening questionnaires will not be eligible for the study. As we are mainly concerned with Opioid Use in our study demographic, we do not anticipate too many participants in our 80 person sample indicating high suicidal ideation, believe that our referral process will be sufficient.

b. Confirm that risks to subjects have been minimized, by use of procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk:

The study teams believes that they have taken the necessary precautions to ensure the safety of our participants.

Protection of Privacy. Participants' privacy will be safeguarded by fully informed consent by informing participants what data will be collected, who will have access to this information, and how knowledge of how information collected will be utilized and disseminated.129 All participants must demonstrate comprehension (full understanding of study details), competence (ability to provide consent), and voluntariness (consent of their own volition) based on their phone calls with the postdoctoral fellow. Following suggestions for fully addressing privacy concerns in digital phenotyping studies, consent will be obtained through verbal discussion with a postdoctoral fellow

using clear, concise language130,131 and will include a short quiz to assess participants' understanding of the potential risks (as suggested by NIMH). 132 To protect participant privacy, we use a speech detection system that does not record raw audio on the device, but, instead, destructively processes the data in real-time to extract, classify, and store features that are useful to infer the presence of human speech but not enough to reconstruct conversation content. Similarly, to protect participant privacy, we do not record any content of calls or texts, only the times in which the calls and texts occurred. Notably, the study team has consented tens of thousands of participants in clinical populations by informing them of these data signals.

Exclusion of High-Risk Populations. The current study will exclude persons who will be at high risk, specifically those with: (1) active suicidality, (2) psychosis, and (3) bipolar disorder. Treatment referrals will be made to those persons (see Clinical Referrals below).

Clinical Expertise and Supervision. All clinical assessments will be carried out by a postdoctoral fellow with a Ph.D. in clinical or counseling psychology using phone calls. Note persons who receive their Ph.D.'s in clinical and counseling have received years of training in clinical assessment and accrued 500 hours of patient contact prior to a predoctoral clinical internship and 1,500 hours of clinical experience on a clinical internship prior to graduating, as mandated by the American Psychological Association. The postdoctoral fellow will be given additional standardized training and supervised by Dr. Jacobson. All clinical assessments will be digitally recorded allowing assessors to be closely supervised by the research team. The postdoctoral fellow will make every attempt to help make the participants feel comfortable when discussing sensitive material. Importantly, telephone interviews themselves are associated with decreased distress compared and has been recommended to conduct interviews around sensitive topics.136 Building on their clinical training and expertise, the postdoctoral fellow will be trained to respond with empathy and care, to ask follow-up questions that are relevant to the participants' responses and background, and to allow the questions to proceed at a comfortable pace (i.e., allowing time for silence, thought, reflection, and processing of this information).136

Availability of the Study Team. Dr. Jacobson will be available to discuss the study or any concerns about the study with participants if requested by the participant and/or postdoctoral fellow. Dr. Jacobson will be available in the event of a clinical emergency, and this availability will be clearly communicated orally and in writing to study participants. Participants will be given a letter from investigators with information such as how to reach the investigators in the event of a clinical emergency. Participants will be referred to a treatment resource or a higher level of care if needed (i.e., hospitalization). Participants will be referred to a higher level of care if there is evidence of (1) acute active suicidality with a plan and intent to take one's life within a delineated period of time (i.e. less than 1 year), (2) acute homicidally with a plan or intent to take another's life, or (3) likelihood that they could immediately cause severe bodily harm to themselves or others (see Clinical Referrals below).

Ability to Withdraw. Participants may be able to withdraw from the study due to a significantly deteriorating course (e.g., need for hospitalization) or if the PI or participant determines that staying in the study is not in the participant's best interest. All participants who withdraw will be provided referrals for treatment.

Quality Control of Online Screen Data. To exclude duplication and ensure validity, Qualtrics checks every IP address and uses unique and sophisticated digital fingerprinting technology that is continuously being improved. Qualtrics is committed to providing the highest quality data to their clients. Qualtrics will replace respondents who finish less than half of the median survey completion length. Qualtrics also provides clients the opportunity to review the results and contact the Qualtrics team to request responses that need to be replaced, should there be any quality issues.

Data Security. All data on phones, on the server, and in-transit (including data sent from the wearable device to the phone) will be encrypted using industry standards (based on a 2048-bit encryption key; only the server can decrypt the data; and the data are physically stored on Amazon S3 data center servers protected by armed guards). The data collection and server storage are both fully HIPAA compliant.

Clinical Referrals. All participants will be given the phone number for the National Suicide Prevention Hotline, which is funded by the Substance Abuse and Mental Health Services Administration (SAMHSA). The hotline is staffed 24/7 by licensed mental health providers and is available throughout the United States. For persons not in acute risk who need a referral to outpatient treatment, we will identify referral sources using the Anxiety and Depression Association of America (ADAA), the Association for Behavioral and Cognitive Therapies (ABCT), the American Psychiatric Association, and the American Psychological Association. Each of these organizations maintains an active registry of current psychologists and psychiatrists across the country, many of whom provide the ability to also specify persons specializing in treating MDD. Participants in acute psychiatric emergencies will be directed to travel to their nearest emergency room,

Plan to Report any Participants Experiencing Potential Crisis:
All incidents of participants experiencing potential crises where follow-up is required will be reported within a week via email to CPHS, including a description of the action taken.

c. Describe why all the risks to subjects are reasonable in relation to both anticipated benefits and the knowledge expected to be gained from the study:

3. Potential Benefits of the Proposed Research to Human Subjects and Others
There are several potential benefits of the proposed research. Participants may experience reductions in their anxiety and depressive symptoms, as well as decreased cravings and reduced opioid use behaviors. In addition, there are also some salient potential benefits to other persons with anxiety and depressive disorders and OUDs based on the results from this work. In particular, this work could foster the ability to deliver behavioral treatments with little cost to persons needing treatment.
4. Importance of the Knowledge to be Gained
The knowledge to be gained from the proposed project has substantial public health importance. Anxiety and depressive disorders are common, severely disabling, and costly conditions. Thus, the current proposal will fill a crucial gap in knowledge regarding whether technology-based interventions for anxiety and depressive disorders might be used to improve treatment among persons receiving medication treatment for OUDs.

7. Unexpected Events or Incidental Findings

Note: It may be important to consider the potential for certain unanticipated events to occur, for example:

- finding an anomaly in a MRI
- discovering child abuse
- causing distress in interviews of a sensitive nature

Describe potential events and provide a plan of action:

Dr. Jacobson will be available to discuss the study or any concerns about the study with participants if requested by the participant. Dr. Jacobson will be available in the event of a clinical emergency, and this availability will be clearly communicated orally and in writing to study participants. Participants will be provided information such as how to reach the investigators in the event of a clinical emergency.
Participants will be referred to a treatment resource or a higher level of care if needed (i.e., hospitalization). Participants will be referred to a higher level of care if there is evidence of (1) acute active suicidality with a plan and intent to take one's life within a delineated period of time (i.e. less than 1 year), (2) acute homicidally with a plan or intent to take another's life, or (3) likelihood that they could immediately cause severe bodily harm to themselves or others (see Clinical Referrals below).
Ability to Withdraw. Participants may be able to withdraw from the study due to a significantly deteriorating course (e.g., need for hospitalization) or if the PI or participant determines that staying in the study is not in the participant's best interest. All participants who withdraw will be provided referrals for treatment.
Clinical Referrals. All participants will be given the phone number for the National Suicide Prevention Hotline, which is funded by the Substance Abuse and Mental Health Services Administration (SAMHSA). The hotline is staffed 24/7 by licensed mental health providers and is available throughout the United States. For persons not in acute risk who need a referral to outpatient treatment, we will identify referral sources using the Anxiety and Depression Association of America (ADAA), the Association for Behavioral and Cognitive Therapies (ABCT), the American Psychiatric Association, and the American Psychological Association. Each of these organizations maintains an active registry of current psychologists and psychiatrists across the country, many of whom provide the ability to also specify persons specializing in treating anxiety and depression.

8. Placebo Use or Inconsistency with Standard of Care

Does any part of this study involve the use of a placebo or procedures that are inconsistent with the standard of care?

☒ **No** ☐ **Yes**

If Yes, explain how the use of placebo or non-standard of care therapy may affect risks for participants, addressing the following:

- The safety and efficacy of other available therapies
- The maximum total length of time a participant may receive placebo on study
- The greatest potential harm that may result from not receiving or delaying effective therapy
- Safeguards for the participants receiving placebo or non-standard of care therapy

n/a

9. Genetics

Does any part of the study involve genetic analysis of biological specimens?

☐ **No**

☐ **Yes,** the study is based on the premise that a link between a genotype or a biomarker and a specific disease or condition is clinically useful in predicting the development of that specific disease or condition. **Please complete the Genetic Research Form and upload it to the 'Supporting Documents' page in Rapport.**

-OR -

☒ **Yes,** the study is looking for an association between a genotype or a biomarker and a specific disease or condition, but at this point it is not clear if the genetic marker has predictive value. The uncertainty regarding the predictive value of the genetic marker is such that studies in this category will not involve referral of participants to genetic counseling; however, participants will be informed of genetic testing in the consent form. **Please comment:**

We ask participants to take urine samples throughout the course of the study. We will send participants urine tests to their physical address. Then we will ask participants to take pictures of the urine tests and send them to the research team. Participants will have access to their results, but the study team will not collect any physical bio samples, just pictures of the urine test results.

10. Equitable Participant Selection

a. Estimated number of participants at Dartmouth CPHS reviewed sites:

The research team hopes to enroll 80 participants

b. Provide a justification of the proposed sample size

Participants will be recruited from an online study based on Google Adwords and Facebook advertisements as online recruitment has been shown to be a viable and cost-effective recruitment method for opioid users (Marshall et al., 2018).

c. Define the target population:

The participants will currently be receiving treatment for opioid use disorder. Additionally, participants must meet the following criteria: (a) Adults (age 18 or older), (b) fluent in English, (c) able to provide informed consent, (d) meet current criteria for OUD (as defined by a Rapid Opioid Dependence Screen), (e) are receiving methadone, buprenorphine, and/or naltrexone for OUD, and (f) meet current criteria for an anxiety and/or depressive disorder (based on the Patient Health Questionnaire and the Generalized Anxiety Disorder Questionnaire).

d. Vulnerable populations

Note: Certain populations are considered vulnerable to coercion and undue influence and are provided with additional protections when participating in a research study.

Identify any of the below populations which you plan to recruit for this study. In addition, complete the form(s) linked with each population as necessary and upload on the 'Supporting Documents' page in Rapport.

☐ Pregnant Women, Fetuses and Neonates
☐ Children
☐ People with impaired decision-making capacity

The following populations may also be considered vulnerable to coercion or other undue influence:

- Prisoners
- People who are economically disadvantaged
- The elderly
- People who are illiterate or do not speak English
- Students and employees

Describe any other potentially vulnerable population(s) and the additional protections provided to them:

We will not be recruiting vulnerable populations. All the participants will have the capacity to make informed consent.

11. Recruitment

Describe method(s) of recruitment. Associated advertisements and other materials to be used for recruitment should be uploaded to the 'Consent Forms and Recruitment Materials' page in Rapport.

The research team will recruit participants using Google Adwords and Reddit. Please see attached document for the advertisement that will be used. The add will contain a Qualtrics link that the participant can click on to access more information about the study and to sign up.

12. Informed Consent, Assent, and Authorization

All forms discussed in this section should be uploaded to the 'Consent Forms and Recruitment Materials' page in Rapport

a. Please describe the consent and/or assent process, addressing the following:

- Who will obtain consent/assent from participants
- Where the consent/assent process will take place
- The timeframe for providing information potential participants about a study, having the consent form signed, and beginning study activities
- Any precautions taken to minimize the possibility of coercion or undue influence
- The forms which will be used as well as any aids used to simplify scientific or technical information
- How comprehension will be ensured

Participants will be recruited online from Google Adwords and Reddit advertisements. If interested, participants will be prompted to click on the Qualtrics link for the consent form to fill out the screening questionnaires to see if they are eligible. Participants will be given screening questionnaires which include the Rapid Opioid Dependence Screening form and Opioid Craving Scale. Participants will also give permission to collect and keep contact information in this initial screening consent form. They will be prompted to give basic contact information such as name, telephone number, email address, and mailing address. If participants are eligible based on their answers to their responses to the screening questionnaires, they will receive the main consent form. Participants will receive an overview of the study containing the following information: (a) the nature of the study in its entirety, including both information about the questions asked during the screen,(b) data storage and retention plan, (c)who will have access to this information, and (d) research team contact information for any questions that the participant may have. Once participants have had all their questions answered and have read over the study summary and seen the info sheet, they will be prompted to sign the consent form electronically via Qualtrics link. All consent forms will be stored on a secure Dartmouth server that is password protected. Participants will also be able to access the Qualtrics link at all times and be able to scroll back and forth through the consent form.

b. Waiver(s) or alteration(s) may be requested for research that involves no more than minimal risk.

Indicate requested waiver(s) or alteration(s) below. In addition, complete the corresponding section of the Waivers and Alterations Request Form and upload it to the 'Consent Forms and Recruitment Materials' page in Rapport.

- ☐ For the informed consent *process*
- ☒ For the *documentation* of informed consent
- ☒ For the HIPAA Authorization to use and/or disclose PHI
- ☐ For a waiver of the requirement for medical record documentation

13. Financial impact on participants

a. List the tests, visits, and procedures performed for only research purposes and specify who will pay:

Note: Research procedures may not be billed to a health insurance plan

Participant Recruitment. A total of $3,000 will be spent on online participant recruitment in the US only. We estimate a total cost of $10 per participant to recruit 3000 participants, with an estimated enrollment of 2% of persons who complete the screen will enroll in the primary portion of the study. **Precision Dx 12-panel Urine Tests.** The Precision Dx 12 Panel Cup test cups will cost a total of $2,250.00 to purchase (we will need to purchase 300 units, with 25 units per case, we will need to purchase 12 cases with each case costing $187.50). To save on shipping costs, the five tests will be mailed together to participants in one box. Participants will be asked to send a picture of the results label to save on shipping costs and so that no bodily fluids are traveling via mail. There will be an estimated $720 in shipping costs.

Participant Remuneration: Participants will be paid $15 for each pre, post, and follow-up questionnaire assessment and $15 for each urine test (totaling $120 per participant). Thus, the total cost requested for participant payment is $7,200.

14. Compensation or Gifts

Please describe any payments, gifts or reimbursements participants will receive for taking part in the study:

Participants will be compensated via amazon giftcard for each component of the study they complete. They will receive 15 dollars for each questionnaire assessment they complete along with 15 dollars for each completed urine test. Compensation will be pro-rated if participants forget to complete any part of the study: The following information lays out the time points that participants will be compensated. Participants will not be compensated for completing the screening questionnaires.

Before the Digital Intervention: 30 dollars total
1) $15 dollars for completing the self-assessment survey
2) $15 dollars for providing the first urine (after 0 weeks) sample results.

After the Intervention is completed: 45 dollars total
1) 15 dollars for completing the post-intervention questionnaire
2) $15 dollars for providing second urine sample (after 2 weeks)
3) $15 dollars for providing third urine sample (after 4 weeks)

At the one-month follow-up: 45 dollars total
1) $15 dollars for completing one-month follow-up post measures
2) $15 for providing fourth urine sample results (after 6 weeks)
3) $15 for providing fifth urine sample results (after 8 weeks)

15. Privacy of Participants

Note: Methods used to obtain information about participants may have an effect on privacy. For example:

- Consent discussions or interviews held in public which concern sensitive subjects or behaviors
- Observations of behavior, especially illicit behavior, in quasi-public settings

Describe any activities or interactions which could lead to a breach of privacy and provide a plan to protect participant privacy:

All Participants data will be collected and stored under a unique identifier. Any files linking the participant information and their study data will be stored on a password protected Dartmouth server. Participants' privacy will be safeguarded by fully informed consent by informing participants what data will be collected, who will have access to this information, and how knowledge of how information collected will be utilized and disseminated (Ziegeldorf, García-Morchón, & Wehrle, 2014).

16. Confidentiality of Data

Note: Any person engaged in research collecting information that could cause financial, social or legal harm to participants may apply for a Certificate of Confidentiality. Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They are intended to allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.

a. If disclosed, could any of the data collected be considered sensitive, with the potential to damage financial standing, employability, insurability, or reputation?

☐ **No** ☒ **Yes**

If Yes, describe the data or information, the rationale for their collection, and whether a Certificate of Confidentiality will be obtained:

Since we are collecting data about opioid addiction and urine test results, these results could potentially damage employability, reputation, and insurability. The research team believes that creating no-cost, scalable interventions for populations suffering from opioid addiction is an important step in advancing treatment for this population.

b. Describe the safeguards employed to secure, share, and maintain data during the study, addressing any of the following which may apply:

- Administrative, ie. coding of participant data
- Physical, ie. use of locked file cabinets
- Technical, ie. encrypted data systems

All data will be stored on a password protected Dartmouth server. We will use a two-document system. The coded identifier form will contain both the Study ID and any identifiable data from the participant. This data includes name, DOB, phone number, email, address and any other contact information collected during the study. This form will be destroyed at the end of the study. The second is the Data element form, which will contain any study information collected (pictures of the urine test results, assessments, and smart phone data)

c. Describe the plan for storage or destruction of data upon study completion:

Data will be preserved for the duration of the study. Once the study if completed the coded identifier form which is the document that connects the participant ID with their contact information will be destroyed. However, all data collected for the duration of the study will be kept indefinitely until it is no longer needed. All results will be stored on a password protected server which will only be accessed by study team members.