STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Print Close

IRB_00141495

1. Contacts and Title

2/27/2021 11:56 AM

PI: Eric Garland PhD/Associate Professor and Associate Director of Integrative Medicine

Submitted: 3/9/2021

Title: Digital Therapeutic Development of Virtual Cognitive-Affective Training for Opioid Use Disorder

1. Study Introduction

1.

a. **Position of the Investigator:**

- ◆ **Faculty or** Non-Academic Equivalent
- ☐ Student
- ☐ Staff
- ☐ Resident/Fellow
- ☐ Other

2. **Contact Persons for the Responsible Investigator:**

Name	Email	Training

3. **Guests of the Responsible Investigator:**

Last Name	First Name	E-Mail

There are no items to display

4. **What type of application is being submitted?**

New Study Application (or Amendment/Continuing Review)

5. **Title Of Study:**

Digital Therapeutic Development of Virtual Cognitive-Affective Training for Opioid Use Disorder

6. **Study Purposes and Objectives:**

The US is experiencing an opioid crisis, with an estimated 2.5 million Americans meeting full criteria for opioid use disorder (OUD)[1] and another 10.3 million who misuse prescription opioids (i.e., have subthreshold OUD).[1] In 2017, more than 70,000 people died from drug

overdoses in the US, approximately 70% of which involved opioids.[1] Medication for opioid use disorder (MOUD) is currently the most effective intervention for OUD; MOUD such as buprenorphine are currently being delivered in tandem with adjunctive behavioral therapies in opioid treatment programs (OTPs) throughout the country.

In spite of the proven efficacy of MOUD, 42% of people who begin an MOUD discontinue them within 24 weeks[2] and 50% of people retained in MOUD have an opioid relapse within six months.[3] As such, novel and efficacious behavioral adjuncts to MOUD are needed to improve adherence to medication, improve treatment outcomes, and reduce relapse in individuals seeking treatment for OUD. The NIH HEAL initiative has focused attention on behavioral research to improve medication-based treatment of OUD. Among behavioral interventions being considered, mindfulness-based interventions (MBIs) have been highlighted by NIH to have particular promise as adjunctive treatments for OUD. However, MBIs and other extant behavioral treatments for OUD require significant face-to-face contact and human resources—barriers to treatment accessibility that also increase the risk of treatment dropout. Therefore, novel treatment strategies are needed to help overcome this crisis. One strategy would include treating OUD with digital health technology in order to improve treatment retention and outcomes. Thus, our overall goal is to develop and pilot test a new digital therapeutic strategy based on an Mindfulness Oriented Recovery Enhancement (MORE), an empirically-supported MBI for OUD. Specific aims for this project are:

Aim 1: To determine the detailed functional, technical, and customization requirements to translate the MORE program into a virtual experience, and to adapt therapeutic material from the published MORE treatment manual[66] so that it can be delivered via a virtual reality (VR) platform. This program will be referred to as MORE-VR.

Aim 2: The MORE-VR prototype will be developed from the program designed in Aim 1. Initial testing of the prototype will be conducted by patients to evaluate safety, usability, and satisfaction– as well as changes in proximal outcomes (*opioid craving, positive affect*).

7. **Is this a multi-site study, where more than one site needs IRB approval?**

☐ Yes ☐ **No**

8. **Background and Introduction:**

MOUD treatment outcomes may be subverted by the allostatic effects of opioids on brain stress and reward circuitry. Allostatic models posit that prolonged use of opioids to alleviate affective distress may shift hedonic set points in corticostriatal brain circuitry mediating reward and disrupt emotion regulatory capacity, compelling opioid use as a means of preserving a dwindling sense of well-being. Thus, OUD involves a process of hedonic homeostatic dysregulation, in which the motivation to obtain natural rewards is re-organized around seeking drug-associated reward and the desire to alleviate aversive states (e.g., affective distress).[4] Consequently, opioid-related cues come to usurp the salience of cues predicting natural, non-drug rewards, evident by heighted opioid cue-reactivity in corticostriatal circuitry including orbitofrontal (OFC) and anterior cingulate cortex (ACC); and the ventral striatum (VS)[5–7] - propelling opioid craving and relapse.[8,9] Unfortunately, among people treated with MOUD, blunted reactivity to non-drug rewards has been observed in brain regions including the dorsolateral prefrontal cortex (PFC)[10] and ventral striatum[11] – suggesting that reward deficits remain untreated by the most effective first-line medications for OUD. Further, a recent review found that there are no efficacious pharmacotherapies for treating opioid-related reward deficits.[12] As such, to improve outcomes among people with OUD, novel interventions are needed to remediate hedonic dysregulation in brain reward circuitry.

To that end, Mindfulness-Oriented Recovery Enhancement (MORE), a cognitive training intervention generated by a NIDA-funded treatment development process (R03→R34→R01), has shown significant promise. Rooted in affective neuroscience, MORE unites training in mindfulness, reappraisal, and savoring skills to remediate dysregulation in brain reward systems underpinning opioid misuse and OUD. In one Stage 1 (N=30)[13] and two Stage 2 RCTs (N=115[14] and N=95[15]), as well as in a newly completed R01-funded Stage 2/3 RCT (N=260), MORE significantly decreased opioid misuse and opioid craving by modulating opioid cue-reactivity and amplifying natural reward processing in the brain[16] , demonstrating the efficacy of the face-to-face intervention for OUD. Yet, the MORE intervention, which must be delivered by trained clinicians, requires significant human interaction and is therefore resource intensive. Further, in light of the COVID-19 pandemic, people with OUD may be reticent to engage in face-to-face interventions due to the risk of viral spread.

Virtual reality (VR) can overcome these implementation barriers. VR environments help serve to reduce the logistical, social, and psychological barriers to MBIs and traditional learning environments (e.g., traveling to a specific place, feeling self-conscious while practicing mindfulness, or stigma associated with the intervention). Also, VR avatars will provide a supportive learning community for self-guided learners who need structure when establishing a new routine such as regular mindfulness practice. An additional benefit of VR is that it is more scalable and disseminable compared with human teachers and usual "brick and mortar" learning environments. Given recent technological advances and associated decrease in cost of VR hardware, VR may be readily accessed in a variety of environments. The ability for a user to access VR-driven digital therapeutics in a clinic and then to have continuity of that intervention in the home environment may facilitate repetition of skill practice, consolidating learning and potentially boosting therapeutic neuroplasticity.[17,18]

In that regard, the premise of this application is that delivering MORE via virtual reality (MORE-VR) will provide an efficacious and highly disseminable form of this evidence-based intervention to improve MOUD outcomes. In addition to overcoming implementation barriers, VR tcan aid in mindfulness-based cognitive and affective training by removing sensory distractions that may otherwise hinder the learning process, personalizing patient experience with machine learning and biometric feedback, and encouraging interaction and imagination in an immersive virtual environment.[19,20] Through these features, VR will increase the perceived usability of the intervention,[21] helping to bridge the gap between in-person and digital learning environments and increasing treatment engagement.[22,23]

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2. Study Location and Sponsors

1. **Add all locations applying for approval of research via the University of Utah IRB or Human Research Protection Program (HRPP).**

   Click the appropriate button(s) below to add locations:

	Site Name	Investigators Name	Covered Entity	Sub Sites
View	University of Utah	Eric Garland	No Yes	

2. **Will a Central IRB (CIRB) or Single IRB (SIRB) model be used for review of this study for the sites listed in this application?**

   ☐ Yes ☐ **No**

3. **Indicate the source(s) of funding obtained or applied for to support this study.**

	Sponsor	Sponsor Type	Sponsor Contact Information	Prime Sponsor	Prime Sponsor Type	OrgID
View	BEHAVR	Industry		NIH NATIONAL INSTITUTE ON DRUG ABUSE	Federal Government	00018365

4. **Does this study have functions assigned to a Contract Research Organization (CRO)?**

   ☐ Yes ☐ **No**

5. **Does this study involve use of the Utah Resource for Genetic and Epidemiologic Research (RGE)?**
   Examples: Utah Population Database (UPDB), Utah Cancer Registry (UCR), All Payers Claims Database (APCD), etc.

   ☐ Yes ☐ **No**

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Addition of a Site

1. **Site Name:**
   University of Utah

2. **Site Principal Investigator**
   ☐ **Mark if Same as Responsible Investigator (syncs with investigator on the first page)**
   Eric Garland

Email	Training	CoI Date
eric.garland@socwk.utah.edu	9/20/2021 MCG	12/29/2022

   a. **Position of the Site Principal Investigator**
   Faculty or Non-Academic Equivalent

   b. **Will the Site PI consent participants?** ☐ Yes ☐ **No**

3. **Site Contact Persons, if different from the Site PI:**
   ☐ **Mark if Same as Contacts for Responsible Investigator (syncs with contacts on the first page)**

Name	Email	Training
Julia Mills	julia.mills@utah.edu	9/14/2021 MCG

4. **Site Staff and Sub-Investigators**

Name	Email	Training	Obtaining Consent	CoI Date

Name	Email	Training	Obtaining Consent	CoI Date

5. **Site Guests:**

Name	Email	Training

There are no items to display

6. **Select HIPAA coverage for this study:**

Study procedures will be conducted within a HIPAA Covered Entity at this site (HIPAA Privacy Rule applies)

Study procedures will be conducted outside a HIPAA Covered Entity at this site (HIPAA Privacy Rule does not apply)

7. **Select the study procedures that will be conducted at this site:**

Recruitment

Consent/Enrollment

Research observation/intervention with participants

Data collection

Data analysis

Do you have an enrollment goal or anticipated enrollment number for this site?

◆ **Yes**

☐ No

Enrollment Number:

30

8. **Select the University of Utah department responsible for this research:**
COLLEGE OF SOCIAL WORK-DEAN

9. **Add any additional sites that are part of this performance group**
There are no items to display

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Sponsor Information

a. Are you receiving award or contract management for the sponsored funds through the University of Utah Office of Sponsored Projects?

◆ **Yes** ☐ No

If yes, select the associated OSP Proposal ID/DSS through eAward to link it to the ERICA system.

You must have a fully approved Proposal ID/DSS number through eProposal which will show up in eAward after OSP has integrated the ID. To access the eAward application, use the instructions on the OSP website.

Link to a Proposal ID/DSS through eAward

Proposal ID/DSS: 10058817
PI: GARLAND,ERIC L
Sponsor: BEHAVR
Prime Sponsor: NIH NATIONAL INSTITUTE ON DRUG ABUSE
Department:
Short Title: BEHAVR R43/R44 SUBAWARD
Sponsor Award Number: 10058817
Type: Industry
Award Start Date: 5/15/2021
Award End Date: 4/30/2022
Prime Sponsor Type: Federal Government

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3. Participants

1. **Ages of Participants:**

   18 and older (Consent form needed)

2. **Specific age range of participants (e.g., 7-12 years old, 60+, etc.):**
   18+

3. **Indicate any vulnerable participant groups (other than children) included:**

   None

   If "Other", please specify:

   If "None" and no children are involved, answer the following question.
   Has the participant selection process overprotected potential subjects who are considered vulnerable so that they are denied opportunities to participate in research?
   ☐ Yes ☐ **No**

4. **Number of participants to be included and/or enrolled in this entire study, across all study locations:**30 enrolled; 1000 screened

5. **Characteristics of Participants/Inclusion Criteria:**

   Inclusion criteria: 1) Men/women 18+ years of age, 2) current DSM-5 Opioid Use Disorder diagnosis as assessed with the Mini-International Neuropsychiatric Interview (MINI), and 3) in treatment for opioid use disorder.

6. **Participant Exclusion Criteria:**

   1) Mindfulness intervention experience, 2) active psychosis or suicidality on the MINI); 3) reports, or is noted by clinical or study staff as showing cognitive impairment; 4) unwilling or unable to remain in OUD treatment for the duration of the trial (e.g., planned relocation, pending incarceration, etc.).

7. **Is a substantial percentage of the participant population anticipated to be non-English speaking?**

   ☐ Yes ☐ **No**

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4. Study Information

1. **Design of Study (select all that apply):**

☐ **Non-Experimental and/or Descriptive Research Design:**

There are no items to display

☐ **Experimental and/or Interventional Research Design:**

Prospective Biomedical Intervention or Experiment

☐ **Development of a research resource (repositories, databases, etc.)**

There are no items to display

☐ **Other**

2. **Does your study involve the use of any placebo?**
☐ Yes ☐ **No**

3. **Length of entire study, from initiation through closeout:**
15 months

4. **How will participants be recruited or identified for inclusion in the study?**

a. **Select all methods that will be used:**

In-person contact (e.g., patients, students, etc.)

Referrals

Written or electronic record review

Written advertising (flyers, brochures, website postings, newspaper ads, etc.)

b. **Describe the recruitment/participant identification process in detail (e.g. who will review charts or records, who can refer participants to the study, where will flyers be posted, how often will recruitment letters be sent, when will follow-up phone calls be made, etc.):**

Recruitment efforts will be focused on reaching potential participants at the University of Utah health care system, and Highland Ridge Hospital, a substance use outpatient treatment program serving ~360 unique OUD patients a year. We will also recruit participants from other OUD treatment programs in the Salt Lake Valley. Participants may be referred to the study from a healthcare provider, or may self-refer after reviewing study marketing materials. We will work closely with provider partners within the University of Utah, from Highland Ridge Hospital, and other OUD treatment providers to educate staff regarding the study, establish referral processes, and provide marketing materials.

In addition to marketing within the healthcare environment, advertisements, marketing materials, and website links may be displayed at community locations or posted on media platforms of interest to the general community. Marketing materials include those attached in the documents and attachments section of this application.

Provider Referrals

A provider may choose to refer a potentially eligible participant directly or provide marketing materials for self-referral. If a provider gives a referral to the study team directly, he or she will be trained to ask permission from the patient for the study coordinator/assistant to contact them prior to sending contact information to the study team.

We will also use the Enterprise Data Warehouse (EDW) at the University of Utah to identify potentially eligible participants through an initial search and will receive updated information on an ongoing basis. We will also use the Human Subjects Recruitment Tool to identify potentially eligible participants. Participants identified by the EDW or Human Subjects Recruitment Tool will first be sent an introductory letter via MyChart prior to being contacted by a member of the study team inviting them into the study.

Self-Referral

Potential participants will have multiple avenues for self-referral after learning about the study.

- Call a research coordinator/assistant
- Email a general inbox to reach a research coordinator/assistant
- Click a link to our website: www.socialwork.edu/painstudy
- Scan a QR code with their smartphone camera
    - This option connects the participant with a pre-screening survey that allows them to gain more information about the study and answer a few short questions to determine eligibility, and then leave their contact information for study personnel.

Medical Record Review: For patients within the University of Utah covered entity, the research team has access to medical records and may conduct a chart review once notified of a potentially eligible participant through any of the above methods. Patient name, MRN, date of birth, phone number, address, and email will be recorded for the purpose of recruitment.

Use of the Human Subjects Recruitment Tool (HSRT): The Principal Investigator or his study staff may utilize the HSRT to review the electronic health records at the University of Utah clinics to determine if potentially eligible patients are attending scheduled appointments. If so, the PI, coordinator, or research assistant may attempt to meet the patient at the clinic at the time of their appointment to inform them about the study, pre-screen for eligibility, and schedule a full study informed consent appointment.

No information collected during the study will be added to patient records.

5. **How will consent be obtained?**

Informed Consent Process (with or without a document)

6. **Describe all the procedures chronologically, from screening/enrollment through study closeout, which will be completed in the research project.**

This project is funded by the National Institute on Drug Abuse (NIDA) as a SBIR grant. BehaVR, LLC is the prime awardee and the University of Utah is BehaVR's academic partner for this project, as a subawardee. BehaVR will develop the MORE-VR virtual reality system with funding from NIDA. The University of Utah will conduct an initial pilot test of this system via the proposed study below:

1. A sample of 30 patients receiving MOUD will be recruited from University of Utah Healthcare System, Highland Ridge Hospital, or self-referral.

2. At the time of initial contact with the research team, the Principal Investigator, Study Coordinator, or Research assistant will explain the study and invite potential participants to ask questions. Potential participants will then be screened for eligibility. Psychiatric and substance use disorders will be assessed with the **Mini-International Neuropsychiatric Interview (MINI),** a structured interview with good inter-rater and test-retest reliability.[67] Opioid withdrawal will be assessed with the **Clinical Opiate Withdrawal Scale (COWS)**.[69]

3. Informed consent will be obtained from all eligible participants.

4. Following screening and informed consent, eligible participants will be assessed for baseline clinical characteristics with the **Addiction Severity Index,** the **Depression Anxiety Stress Scale (DASS),** the **Tobacco, Alcohol, Prescription Medications, and other Substances (TAPS),** the **Snaith Hamilton Pleasure and Anhedonia Scale (SHAPS)**, **Metacognitive Processes of Decentering Scale (MPODS),** the **Nondual Awareness Dimensional Assessment,** the **Ways of Savoring Checklist, and** the **Emotion Regulation Questionnaire.**

5. Next, the sample (N=30) will participate in 8 weekly treatment sessions with the MORE-VR system. The VR system consists of commercially available VR goggles (e.g., Oculus Rift) linked with a VR platform consisting of a cloud-based control software that orchestrates the content of VR sessions in real-time. The VR content is based on Dr. Garland's validated Mindfulness-Oriented Recovery Enhancement (MORE) protocol, published in 2013 (Garland, 2013, Mindfulness-Oriented Recovery Enhancement for Addiction, Stress, and Pain. NASW Press: Washington, DC.). Each session of MORE-VR will last approximately 1.5 hours, and a research staff will be present at each VR session, who will teach the participant to use the system and answer any questions that arise.

6. The VR system will capture trace data through logs that capture behavioral engagement with each intervention component. These will include the number of digital object manipulations, clicks, and eye tracking of fixation duration on digital objects

7. At the 8 weekly MORE-VR sessions, the following measures will be administered, for a total of 8 assessments:

a) Craving will be evaluated with a Numeric Rating Scale and the Desires for Drug Questionnaire,[72] and *affect* will be evaluated with the

Positive and Negative Affect Scale (PANAS).[73]

b) Coping self-efficacy will be measured with the Drug Taking Confidence Questionnaire,[74] which predicts heroin relapse.[75]

c) Mindfulness will be evaluated with the Toronto Mindfulness Scale[76] as a therapeutic process measure and manipulation check.

d) Participants will complete a daily symptom diary of opioid craving, drug use and mood symptoms as well as mindfulness skills via ecological momentary assessments (EMA) delivered via the participant's own smartphone or home computer up to 3 times per day (morning, noon and evening).

e) Also at this post-treatment assessment, we will again administer the following questionnaires: **the DASS,** the **TAPS**, **SHAPS**, **MPODS, NADA,** the **Ways of Savoring Checklist, and** the **Emotion Regulation Questionnaire.**

f) Participants will participate in a semi-structured qualitative interview (sample questions attached as an additional document) about the acceptability of the MORE-VR system (e.g., "What did you like best? What didn't you like?" "What would you change?"). The interview will be audio-recorded and transcribed for analysis of intervention acceptability.

g) Safety will be assessed throughout to monitor adverse events.

7. **Are all procedures for research purposes only (non-standard or non-standard of care procedures)?**

◆ **Yes** ☐ No

If no, list the procedures that are performed for research purposes only (non-standard or non-standard of care procedures):

8. **Is there a safety monitoring plan for this study?**

☐ Yes ☐ **No**

9. **Provide a summary of the statistical methods, data analysis, or data interpretation planned for this study. Factors for determining the proposed sample size (e.g., power) should be stated.**

For this Phase I pilot focused on usability, satisfaction and safety, we are not powered to detect a change in proximal outcomes or mechanistic measures. Yet, the repeated-measures nature of our design affords comparatively high statistical power. With 8 measurement points and a moderate repeated measures correlation (r=.30), we will have power of .90 to detect a medium effect size for the simple fixed effect of time (Cohen's f=.25) with N=30. We assume at least a medium effect size based on the large effects of time observed among participants treated with MORE in prior RCTs for craving,[60] $\eta^2_{partial}$ =.24, and positive affect, $\eta^2_{partial}$ =.39.[15]

Safety will be evaluated with the sequential probability ratio test (SPRT)[83] following updated guidelines for small, single arm trials.[84,85] Changes in craving, affect, and physiology (HR, HRV, GSR) across the 8 sessions will be assessed with linear mixed models (LMM) with

Kenwood-Roger degrees of freedom. Simple LMM with small sample sizes can provide unbiased estimates of fixed effects with minimal inflations in type I error.[86] Because this is a non-experimental Phase I pilot study, the fixed effect of time will be the parameter of interest, controlling for OUD severity as a covariate. LMM will specify a random intercept, and random slopes and/or autoregressive repeated covariances if needed and supported by the Bayesian Information Criterion. However, given the small N, we will not over fit models to the point of saturation – models will be simple as possible. Little's MCAR test will determine if data are Missing Completely at Random (an ideal that is rarely met with longitudinal data). There is no definitive test for Missing at Random, which describes data that are random conditional on observed data. We will use restricted maximum likelihood estimation (REML) procedures to deal with missing data according to an intent-to-treat philosophy that is robust against common patterns of missing data. REML is based on all data observations; no values are deleted. Sex differences in treatment response will be examined by including sex as a biological variable of interest in analytic models.

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Consent Process

List by name, role, and affiliation any others who will obtain consent (e.g. Dr. John Smith, Co-Investigator, etc.).

1. **Describe the location(s) where consent will be obtained.**

Center on Mindfulness and Integrative Health Intervention Development, College of Social Work, University of Utah

Highland Ridge Hospital

Consenting via a HIPAA-compliant virtual meeting platform (e.g., Zoom)

2. **Describe the consent process(es), including the timing of consent. Describe whether there is a waiting period between the consent process and obtaining consent from the participant (i.e., any time between informing**

participants and actually obtaining consent).

The consent process will be performed by the study investigators, study coordinator, or research assistants. Dr. Garland will not obtain consent from participants. A potentially-eligible individual will schedule a time to meet with a member of the research staff, either in-person or using a HIPAA-compliant virtual meeting platform such as zoom, at which time the person obtaining consent will explain the protocol in detail and will review and discuss the consent form with the potential participant. The personnel who obtain consent will inform participants of Dr. Garland's financial conflict of interest in this study. If the potential participant appears confused or indicates she does not understand the consent forms, the interviewer will attempt to identify what the individual does not understand and explain the consent again. If the potential participant appears confused or indicates that they do not understand the consent forms, the interviewer will attempt to identity what the individual does not understand and explain the consent again. The potential participant will be offered up to 72 hours to make a decision to participate. If the potential participant elects to enroll, the Principal Investigator, Research Assistant, or Study Coordinator will witness and date the consent after the participant signs.

Consent forms will be signed by the participant and the research team member conducting consent. A copy of the signed consent, including contact phone numbers for the PI and the University of Utah IRB, will be given to the subject. REDCap e-consent framework may be utilized to obtain electronic signatures and distribute signed copies of the consent.

After consent has been obtained, the Coordinator or Research Assistant will schedule participants to begin the study intervention.

3. **Describe what measures will be taken to minimize the possibility of coercion or undue influence.**

Participants will be informed that taking part in this study is their choice. They will be informed that they may choose either to take part or not take part in the study, and if they choose not to participate in this research study, there will be no penalty to them, nor will their decision to participate or not participate affect their eligibility for care or any other benefits to which they are entitled. Participants will be informed that they may also leave the study at any time. They will be notified that if they leave the study before it is finished, there will be no penalty to them, and they will not lose any benefits to which they are entitled.

4. **Describe the provisions that are made to allow adequate time to exchange information and questions between the investigator and participant.**

During the informed consent process, the Principal Investigator, Study Coordinator, or Research Assistant will read, review, and discuss consent forms with all potential participants prior to signing. If the potential participant appears confused or indicates she does not understand the consent forms, the interviewer will attempt to identify what the individual does not understand and explain the consent again. The participant will be informed that there is no rush to complete informed consent and that they should wait until their questions are fully answered before signing.

5. **Will a legally authorized representative (LAR) be used?**

☐ Yes ☐ **No**

7. **Will a language other than English be used to obtain consent?**

☐ Yes ☐ **No**

8. **Are you requesting that documentation of informed consent be waived by the IRB (a consent process in place, but no documentation of consent, e.g. questionnaire cover letter, web-based consent, consent without signature, etc.)?**

☐ Yes ☐ **No**

If yes, complete the following:

a. **Explain why the waiver of consent documentation is being requested.**

b. **Justification for the waiver is one of the following:**

There are no items to display

5. Data Monitoring Plan

1. **Privacy Protections:** Privacy refers to persons and to their interest in controlling access of others to themselves. Privacy can be defined in terms of having control over the extent, timing and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. **What precautions will be used to ensure subject privacy is protected?**

Select all that apply:

- The research intervention is conducted in a private place
- Discussing the study with participants individually instead of in front of a group
- The collection of information about participants is limited to the amount necessary to achieve the aims of the research, so that no unneeded information is being collected
- De-identification of photos, audio tapes, or video tapes of the participant that will be made during the study

Other or additional details (specify):

All materials derived from the study will be handled only by study personnel during collection, storage, and in subsequent data analysis. The PI is experienced in conducting clinical studies and is fully aware of the need for anonymity, privacy and security, and maintains strict surveillance of the office environment. No incidents of violation of patient confidentiality have occurred in the previous studies in which the PI has participated over the past 10 year period.

Protection of Participant Identity and Confidentiality. The following confidentiality protection steps will be taken: 1) all members of the research team will participate in initial training and follow-up training in medical and research ethics; 2) consent forms will be maintained in password protected REDCap databases; 3) any personal identifiers linked to data will be removed and replaced by code numbers in all records; 4) any information suggesting that privacy has been breached will be thoroughly investigated by the PI and reported promptly to the IRB.

Audio-recordings of interviews will be destroyed one year after completion of the project.

2. **Confidentiality Precautions:** Confidentiality is an extension of the concept of privacy; it refers to the subject's understanding of, and agreement to, the ways identifiable information will be stored and shared. Identifiable information can be printed information, electronic information or visual information such as photographs. **What precautions will be used to maintain the confidentiality of identifiable information?**

Select all that apply:

- Storing research data on password protected computers or in locked cabinets or offices
- Participant identifiers will be stored separately from the coded, participant data
- All data that will be transferred or transported outside of the institution will be encrypted
- Destroying photos, audio tapes, or video tapes at the end of the study
- A Certificate of Confidentiality (from the NIH) will be used

Other or additional details (specify):

Identifiers will be removed from participant data, and a key linking participant PHI (name, contact information, birthdate) back to their data will be maintained and stored separately.

3. Will photos, audio recordings, or video recordings, or medical images of participants be made during the study?

◆ **Yes** ☐ No

If yes, describe the recording/images and what will become of them after creation (e.g., shown at scientific meetings, stored in the medical/research record, transcribed, erased, etc.):

The qualitative acceptability interviews will be audio-recorded and transcribed for analysis of the acceptability of MORE-VR. One year after the completion of the study, audio recordings will be destroyed.

4. **How will study data and documentation be monitored throughout the study?**

Select all that apply:

Periodic review and confirmation of participant eligibility

Periodic review of informed consent documentation

Periodic review of the transfer/transcription of data from the original source to the research record

Confirmation that all appropriate information has been reported to the sponsor, oversight agencies (such as the FDA), and/or IRB

Other additional details (specify):

5. **Who will be the primary monitor of the study data and documentation?**

Select all that apply:

Principal Investigator

Study Coordinator or Research Nurse

Research Assistant

Other or additional details (specify):

Other or additional details (specify):

Gary Donaldson, Co-Investigator and Statistician, will also monitor study data.

How often is study data and documentation monitoring planned (e.g., monthly, twice a year, annually, after N participants are enrolled, etc.)?

Quarterly

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6. Risks and Benefits

1. Describe the reasonable foreseeable risks or discomforts to the participants:

All reported symptoms that subjects attribute to the study interventions will be documented and investigated by the PI (who has over a decade of clinical expertise with persons with substance use disorders and chronic pain, as well as clinical research experience through several NIH-funded clinical trials), and reported immediately to the University of Utah IRB. Risks associated with mindfulness meditation are minimal. There is no evidence that mindfulness worsen the symptoms causes complications with opioid therapy. The relaxation experienced as part of mindfulness training is sometimes associated with transient sleepiness, lasting no more than a few hours.

Participation in mindfulness meditation may also increase awareness of anxiety. Participants will be advised to inform the therapists of any significant shift in their symptoms for the worse while taking part in the interventions. Reports of such changes will be given to the PI, who will coordinate to interview the subject and make a determination of need concerning specific medical care or removal from the study. Events of this type are very uncommon, usually transient and pose minor barriers to the completion of this study.

Participants may interpret the interventions as substitutes for usual, conventional medical care. All participants will continue to receive the same medical care from their physician that they would otherwise receive. They will be informed that they should continue such care just as if they were not enrolled in a study. Participants will be asked to inform study personnel if there is a change in medications or other medical care during the trial (both during treatment and follow-up), but patients and their physicians will not be dissuaded from changing medical management practices.

While strict precautions will be implemented to protect patient confidentiality (detailed in the data monitoring plan in section 5 of the IRB application), there is the potential risk of a loss of confidentiality. Because potential participants will be asked about drug use, this could pose a risk to the participants given the illegal nature of their actions.

The consent form will clearly specify that it is the option of the PI and the research team to withdraw a subject from the study should they prove to be a danger to self or others, or a significant disruption to the group. If participants appear intoxicated (as determined by meeting DSM-5 diagnostic criteria for alcohol, cocaine, opioid, amphetamine, or hallucinogen intoxication) or actively suicidal during study assessments or VR sessions, they will not be allowed to continue that session. Instead, they will be referred to the appropriate University of Utah Primary Care Clinic or Highland Ridge Hospital to receive medical evaluation by a physician, brief intervention by a psychologist or social worker, and more extensive mental health services, as needed. Alternatively, if the participant is determined to be a danger to self or others due to suicidal ideation or intoxication, university police will be alerted. Afterward, the PI will contact the participant in question and interview them to determine whether their substance use warrants exclusion from the study.

Another risk relates to the potential for cybersickness, which is a side effect associated with the use of VR technology. Cybersickness is associated with a range of symptoms including nausea, dizziness, disorientation, headaches, sweating, and/or eye strain.

The final risk relates to the measurement protocol. Because the virtual drug cue exposure and negative emotion regulation protocols involve the presentation of opioid- related cues and stressful experiences, there is a risk that they could trigger opioid cravings and psychological distress. Yet, it is very unlikely that such craving or distress will exceed that which would occur on an everyday basis, given that opioid cues (e.g., the sight of a heroin needle) are present in participants' natural environments. To monitor for potential risk, participants will be asked to rate their stress and craving on two 10-point visual analogue scales (1 = none, 10 = extreme) before and after the virtual cue exposure and negative emotional regulation protocols, and then again at the end of the assessment session. In the unlikely event that participants report stress or craving resulting from cue exposure as determined by an elevation in craving or stress by 3 points from baseline levels that maintains at the end of the assessment, the PI will notify the University of Utah IRB, and make a referral for clinical services, as appropriate. To mitigate this risk, the Study Coordinator/Research Assistant (a master's level social worker) will be trained by the PI (a licensed clinical social worker and clinician with over 16 years of experience) to debrief participants, assess risk, and provide 15 minutes of progressive muscle relaxation to ensure subjects have experienced a reduction in stress or craving to a level of within 3 points of their baseline level on the visual analogue scales upon beginning the psychophysiological protocol. In two four RCTs of MORE with persons with substance use disorders, the PI used a similar risk management strategy for a psychophysiological cue-reactivity protocol, and no participants remained distressed after this procedure.

2. **Describe the potential benefits to society AND to participants (do not include compensation):**

While it is possible that there may be no direct benefits to participants, the potential benefits of the research to the participants are significant. Their craving or stress may improve significantly as a result of being part of the study. The process of participating in the MORE-VR could enhance self-efficacy. Participants may learn improved methods of managing OUD from each other's experience. Therefore, it is expected that participants may experience significant benefit from participating in the research study. The potential benefits to other individuals with OUD are also significant. The results of this research may provide credible evidence about the effects of MORE-VR for patients with OUD and whether it may be usefully integrated with conventional care in order to effectively manage opioid misuse and addiction.

3. Are there any costs to the participants from participation in research?

☐ Yes ☐ **No**

If yes, specify:

4. Is there any compensation to the participants?

◆ **Yes** ☐ No

a. If yes, answer the following:

Specify overall amount:
$250

b. Specify when participants will be paid (e.g. at each visit, at end of study, etc.):
Participants will be paid at each visit.

c. If applicable, please specify payment by visit or other time interval (e.g. $10 per visit, etc.):
Participants will be paid $25 for the baseline and post-treatment assessment, $20 per MORE-VR session, plus an additional $40 bonus for completing 5 or more MORE-VR sessions.

d. If applicable, explain plan for prorating payments if participant does not complete the study:
Payment will be prorated according to how many study sessions are completed.

IRB_00141495 | **Created:** 2/27/2021 11:56 AM

PI: Eric Garland PhD/Associate Professor and Associate Director of Integrative Medicine | **Submitted:** 3/9/2021

Title: Digital Therapeutic Development of Virtual Cognitive-Affective Training for Opioid Use Disorder

7. HIPAA and the Covered Entity

1. **Does this study involve Protected Health Information (PHI) or de-identified health information?**
   - ◆ **Yes** ☐ No

   a. **Select the method(s) of authorization that will be used:**

   Waiver or Alteration of Authorization

   b. **Will PHI be disclosed outside the Covered Entity?**
   - ◆ **Yes** ☐ No

   To whom?
   FDA

   And for what purposes?
   Because this study involves the use of an investigational medical device, the FDA may receive PHI.

Does this study involve any of the following:

2. **The investigational use of a drug?**
   ☐ Yes ☐ **No**
3. **The investigational use of a medical device?**
   ☐ Yes ☐ **No**
4. **Is this an investigator-initiated drug or device trial lead by the Principal Investigator?**
   ☐ Yes ☐ **No**
5. **Exposure to radioisotopes or ionizing radiation?**
   ☐ Yes ☐ **No**
6. **A Humanitarian Device Exemption (HDE)?**
   ☐ Yes ☐ **No**
7. **Genetic testing and/or analysis of genetic data?**
   ☐ Yes ☐ **No**
8. **Creating or sending data and/or samples to a repository to be saved for future research uses?**
   ☐ Yes ☐ **No**

9. **Are you:**

- **Collecting samples of blood, organs or tissues from participants for research purposes;**
- **Introducing Recombinant or Synthetic Nucleic Acids (e.g. viral vectors, oligonucleotides) or cells containing recombinant nucleic acids (e.g. CAR-T) into participants; OR**
- **Introducing other biological materials (e.g. bacteria, viruses) into participants.**

☐ Yes ☐ **No**

10. **Does this study involve any of the following?**

- **Cancer Patients**
- **Cancer Hypothesis**
- **Cancer risk reduction**
- **Cancer prevention**

☐ Yes ☐ **No**

11. **Any component of the Clinical and Translational Science Institute (CTSI)?**

☐ Yes ☐ **No**

The Clinical Research Center (CRC)?

☐ Yes ☐ **No**

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Request for Waiver or Alteration of Authorization

Request for Waiver of Authorization for Recruitment Only

This option must only be used if you are reviewing PHI in order to identify eligible participants BEFORE approaching them to obtain consent and authorization. All other waiver requests must be entered below.

Waiver of Authorization for Recruitment Requested

Other Requests for Waivers of Authorization:

- *Click "Add" below to add a new waiver request to this application.*
- *Click the waiver name link to edit a waiver that has already been created.*
- *To delete a waiver request, contact the IRB.*

Date Created	Type of Request	Purpose of Waiver Request
There are no items to display		

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IRB_00141495
Waiver of Authorization for Recruitment Only

Request for Waiver or Alteration of Authorization

Request for Waiver of Authorization for Recruitment Only

The PI must agree to the terms of this waiver request as described on this page. When the PI uses the "Submit" activity to submit the application for IRB review, a checkbox to accept the terms will be available in the "Submit" activity window.

This waiver request includes justification for waivers of consent for recruitment only, according to 45 CFR 46.116(d).

Terms for the Waiver of Authorization:

- The purpose of this waiver of authorization is to allow for the use of PHI in order to identify and recruit individuals who may be eligible to participate in the specific research described in this IRB application. The waiver of authorization is necessary to accommodate this minimal-risk research activity prior to seeking a full authorization from research participants.

- Methods for identifying individuals may include the following:
  - Reviewing medical charts
  - Reviewing databases that include PHI
  - Reviewing other medical- or health-based documents that include PHI

- Identifiable information used under this waiver may include the following, as this is the minimum necessary for identifying eligible individuals:
  - Name
  - Contact information, such as phone number, address, or email address
  - An ID number, such as MRN or SSN
  - Date of birth
  - Medical and health information that may determine study eligibility

- Any PHI recorded by the study team will only be used for recruitment and determining study eligibility. After this has been completed, the PHI must be removed from the research record or destroyed, unless the participants have given authorization for continued use of the PHI.

- PHI will only be viewed by approved members of the study team and will not be disclosed for research purposes to any individual or institution without the participants' authorization for such use and disclosure of the PHI.

- PHI will be stored in a secure manner according to HIPAA privacy and security provisions.

8. Resources and Responsibilities

1. * **State and justify the qualifications of the study staff:**

Utah Principal investigator: Eric Garland, PhD, LCSW, is a licensed clinical social worker with 16 years of post-licensure experience and Associate Dean for Research and Professor, College of Social Work at the University of Utah, Director of the Center on Mindfulness and Integrative Health Intervention Development: oversee all research activities; hire, train, and supervise study staff; triage adverse events; manuscript preparation. Dr. Garland is the developer of MORE who has led 8 successful RCTs and multiple psychophysiological studies of MORE as a treatment for OUD, opioid misuse, and other addictive behaviors.

Gary Donaldson, PhD (Utah Co-I) is Senior Strategic Statistician at University of Utah who has been PI on 5 NIH-funded studies and Director of Biostatistics Core on 2 NIH program projects. Dr. Donaldson will perform blinded statistical analyses of outcome data.

Study personnel: Study personnel include postdoctoral fellows, graduate research assistants, and undergraduate research assistants. All personnel are well-trained in study procedures and have experience in prior clinical trials of MORE and mindfulness for opioid misuse and addiction.

2. * **Describe the training that study staff and investigators will receive in order to be informed about the protocol and understand their research-related duties and functions:**

The entire study team has completed an IRB-approved human subjects training course and is knowledgeable about issues covered in the training. All investigators and research assistants will be trained by the PI on data collection and protocol in handling PHI. The PI has developed a training protocol for research assistants to learn all lab procedures. The training protocol involves:

1. Completing a mock assessment in the role of a "subject" as conducted by trained personnel;

2. Shadowing trained personnel for two assessments with actual participants;

3. Conducting an assessment while supervised by trained personnel until complete proficiency is attained; and

4. data review by the PI to ensure quality data collection with no mistakes

3. * **Describe the facilities where the research activities will be performed (e.g. hospitals, clinics, laboratories, classrooms/schools, offices, tissue banks, etc.).**

A private psychophysiology laboratory at the Center on Mindfulness and Integrative Health Intervention Development (C-MIIND), University of Utah.

A private treatment room at Highland Ridge Hospital.

No data will be shared with external collaborators until all needed agreements are in place with the UU's Partners for Innovation, Ventures, Outreach &Technology, or PIVOT Center.

4. * **Describe the medical or psychological resources available at this site (and other participating sites, if applicable) that participants might require as a consequence of the research. If not applicable, please state.**

Licensed clinical psychologists and licensed clinical social workers are on staff at both locations to provide psychological resources as needed. At Highland Ridge Hospital, physicians and nurses are available to provide medical resources as needed. At C-MIIND, medical resources can be provided by Madsen Health Center, which is a 3 minute drive away.

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Documents and Attachments

If any of your documents (such as investigational brochures, sponsor protocols, advertisements, etc.) are not available in an electronic format, please scan and save them as PDF files or contact our office for assistance.

Naming Documents: Please use the title field to clearly indicate the content of each form. The name you enter will be listed on your approval letter. Use names that will differentiate from earlier versions.

Examples:
Consent Document Control Group 04/14/05
Consent Document Treatment Group 4/14/05
Sponsor Protocol 04/14/05 Version 2
Assent Document(Highlighted Changes)

Apple/Macintosh Users:MS Word documents must have a .doc file extension. See ERICA home page for instructions.

Print View: IRB Draft Protocol Summary

eProtocol Summary:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Consent Documents, Consent Cover Letters, Consent Information Sheets, Consent Scripts, etc.:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Parental Permission Documents:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Assent Documents:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

VA Consent Documents:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Surveys, Questionnaires, Interview Scripts, etc.:

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Full Protocol (company protocol, sponsor protocol, investigator-initiated protocol, etc.):

Name	Version	Date Created	Date Modified	Date Approved
There are no items to display				

Investigational Brochure (IB) for Investigational Drug or Drug/Device Package Insert:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Grant Application:

The Federal Government is a direct or indirect sponsor of your research. You are required to provide a copy of the grant proposal, grant award, or sub-award.

By submitting to the IRB, you are confirming the grant and the study protocol are consistent (Design, Study Population, Study Objectives and Goals, Test Interventions and Procedures, etc.)

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Literature Cited/References:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Principal Investigator's Scholarly Record (CV/Resume):

Name	Version	Date Created	Date Modified	Date Approved
GARLAND_CV_CURRENT_2022.pdf(0.01)	0.01	4/13/2022 8:34 AM	4/13/2022 8:34 AM	

Faculty Sponsor's Scholarly Record (CV/Resume):

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Other Stamped Documents:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Recruitment Materials, Advertisements, etc.:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

Other Documents:

Name	Version	Date Created	Date Modified	Date Approved

There are no items to display

PI: Eric Garland PhD/Associate Professor and Associate Director of Integrative Medicine

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Finish Instructions

Finish Instructions

1. **To view errors, select the "Validate" option at the top-left of the page. If you have errors on your application, you won't be able to submit it to the IRB.**
2. **Selecting the Finish button will NOT submit the application to the IRB.**
   You MUST select the "Submit" option on the workspace once you've selected the "Finish" button.
3. **If your study has a faculty sponsor: Once the PI submits the application, it will be sent to the faculty sponsor for final approval. The IRB cannot review the study until the faculty sponsor submits the application to the IRB.**