Mass General Brigham

Detailed Protocol

Principal Investigator:	David Eddie, Ph.D.
Project Title:	A pilot study of ambulatory heart rate variability biofeedback for substance use disorder
Version Date:	11/27/2023
NCT Number:	NCT05454657

1. Background and Significance

In early SUD recovery, everyday experiences of negative affect and alcohol and other drug cues often serve as triggers for substance use that appear to be automatic in the sense that they bypass patients' cognitive plans and conscious intentions not to use. A central goal of first-line cognitive-behavioral SUD treatments is to strengthen affective and cognitive control to increase individuals' ability to override impulses to use alcohol and other drugs **(AOD)** [1, 2]. Yet, automatic physiological processes compromised by SUD interact with internal affective states and environmental cues to undermine effortful cognitive control and outcompete goals to avoid substance use [3].

In particular, evidence suggests that the baroreflex—the central autonomic network's (CAN) cardiovascular regulatory system that is integral to emotion regulation and goal-oriented behavior—directly participates in substance use maintenance or desistence through its influence on attention capture by provocative cues, cue salience, and visceral reaction to cues [4-6]. Ineffective or maladaptive functioning of the baroreflex is believed to set in motion a cascade of neurocardiac events that alter affect, emotional arousal, and stress response [4, 7, 8] thereby increasing the likelihood that susceptible individuals will seek or use AOD, even following extended periods of abstinence [3, 9, 10]. Moreover, baroreflex inefficiency is strongly interrelated with SUD drivers and corollaries including anxiety, depression, and stress [11-14].

Heart Rate Variability Biofeedback **(HRVB)** is a biobehavioral intervention involving rhythmic breathing at resonance frequency **(RF)** that stimulates the baroreflex to offset these psychophysiological deficits. The autonomic normalization effected by RF breathing is believed to bolster cognitive control efforts by interrupting or dampening automatic-visceral reactions that can unintentionally undermine treatment gains, and in doing so support better decision-making, motivation, reductions in craving, and shifts in attention allocation [15]. HRVB's capacity to help individuals better regulate affect and bolster cognitive control has garnered excitement in addiction clinical science [3, 16, 17], and preliminary studies suggest HRVB could be a valuable addendum to first-line addiction treatments [15, 18-24].

Studies of first-generation HRVB focused on positive cognitive and behavioral effects that accrue over weeks or months of regular, daily RF breathing practice. However, recent studies have demonstrated that a brief exposure to RF breathing in anticipation of psychosocial stress, or during induced stress, helps to control physiological arousal, reduce state anxiety, and improve cognitive performance [15, 25, 26]. Our clinical observations provide further support for in-the-moment

RF breathing. We have observed many HRVB study participants intuitively use RF breathing to manage intense, momentary negative affect, even though they were not explicitly instructed to do so [18, 24]. We posit that such in-the-moment bursts of HRVB practice could be an SUD treatment tool that helps individuals buffer salient triggers and urges to use AOD in-the-moment.

Recent advances in the field have given rise to small, lightweight, wearable biosensors that can allow wearers to do HRVB on-the-go. These second-generation HRVB devices can also function as a just-in-time interventions by prompting in-the-moment HRVB practice when autonomic hyperarousal is detected, to buffer salient triggers and urges to use AOD. In addition to their potential for direct clinical benefit, the advent of these second-generation, ambulatory, HRVB devices has implications for the accessibility and scalability of HRVB because these devices are affordable, accessible, integrate with the end-user's smartphone, and do not require a provider to administer the intervention.

This study builds on a body of preliminary work speaking to HRVB's potential as an addendum to first-line SUD treatments. We will be using the 'Lief Smart Patch' device in this research (https://getlief.com). The Lief Smart Patch is a small, wearable, electrocardiogram (ECG)-based heart rate monitor that is attached to the body utilizing skin safe ECG electrodes. ECG technology is known to be safe and carries no substantial risk. The device monitors heart rate variability (HRV) as an index of autonomic nervous system arousal and can prompt the wearer to engage in brief bursts of HRVB practice via a connected smartphone app when stress is inferred. Wearers are also able to engage in regularly scheduled HRVB practice, and practice *ad libitum*. The Lief biofeedback device is being used in this study to deliver a clinical intervention and collect physiological data; the effectiveness of the device itself is not being tested.

2. Specific Aims and Objectives

The aim of this pilot study is to administer heart rate variability biofeedback (HRVB) to adults with substance use disorder who are receiving outpatient treatment as usual (TAU) and compare them to a control group receiving TAU only on intervention outcomes that include alcohol/drug use and negative affect. The study's specific aims are as follows:

Aim 1: Assess ambulatory HRVB's uptake by individuals with SUD in terms of practice time, and perceived barriers to uptake based on qualitative participant feedback (proof-of-concept)

Aim 2: Test effects of HRVB practice on affect and substance use

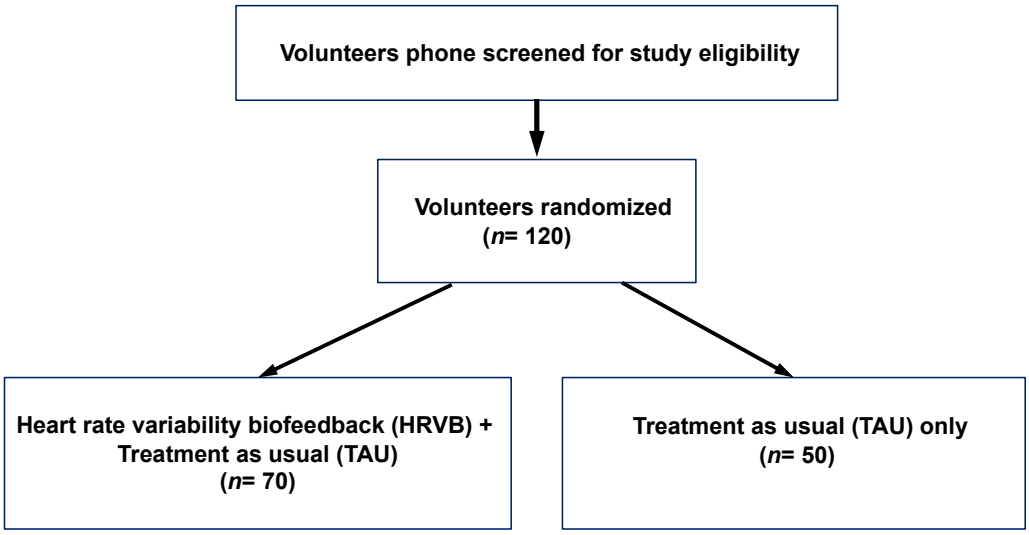
- **a.** Test day-level effects of HRVB practice on affective states and substance use
- **b.** Test the accumulative, person-level effects of scheduled daily HRVB practice vs. in-the-moment HRVB practice, vs. their interaction on substance use during the 8-week intervention period

We hypothesize that participants receiving HRVB + TAU will have a lower alcohol/drug use lapse rate and demonstrate greater reductions in negative affect compared to controls receiving TAU only.

3. General Description of Study Design

Design Overview

We will recruit 120 adults with substance use disorder (SUD) in their first year of a current SUD recovery attempt. Participants will be randomized using the SAS statistical program to either the experimental (*n*= 70) or control group (*n*= 50). We will also recruit 10 experimental group participants to participate in focus groups (*n*= 5 in each).



Experimental group participants will participate in 8 weeks of HRVB training using the Lief HRVB biopatch and smartphone app, and 2x daily ecological momentary assessment of affect and substance use. Participants will also be encouraged to self-initiate ecological momentary assessment surveys when feeling high levels of stress or craving. Experimental group participants will be encouraged to wear the Lief HRVB biopatch for at least 8 hours per day and use it as needed to regulate negative affect in-the-moment with a minimum of 5mins daily *ad hoc* practice, and 5min of scheduled HRVB practice twice daily, for a total of 15min daily practice.

The control group will participate in 8 weeks of 2x daily ecological momentary assessment of affect and substance use. Participants will also be encouraged to self-initiate ecological momentary assessment surveys when feeling high levels of stress or craving. Both groups will be allowed to continue with whatever SUD treatment they are independently engaged in. In other words, we will not ask participant to desist any existing treatments they are utilizing.

4. Subject Selection

Participants

Participants will be 120 adults ≥18 years of age in the first year of a current SUD recovery attempt. To reduce the likelihood of acute substance withdrawal symptoms influencing affect and physiological indices, participants will be required to have at least two weeks of abstinence from alcohol and other drugs immediately prior to study participation. To allow for recruitment of a representative sample of individuals in early recovery from SUD, commonly co-occurring psychological conditions such as affective disorders and PTSD will be allowed. Medications will be allowed. However, individuals with severe cardiac arrhythmias which would confound HRV

analyses will be excluded, as will persons with active psychosis.

Recruitment Procedures
Participants will be recruited via Mass General Brigham HealthCare's RSVP for Health Recruitment system, as well as flyers placed throughout Mass General Brigham Healthcare sites (e.g., Massachusetts General Hospital, Brigham and Women's Hospital, McLean Hospital). Advertisements will also be placed on social media sites such as *In the Rooms* and *Facebook* with chat and comment features disabled in order to protect privacy. Individuals who are interested in participation will be invited to call the study researchers who will explain the study procedures in detail, including the potential benefits and risks and the expected duration and time commitment of their participation. Potential participants will also be able to complete a brief, online, pre-screening questionnaire delivered via REDCap. Individuals who are potentially eligible based on their responses to this form will be contacted by study staff for full phone screening (see 'Subject Enrolment' section below).

5. Subject Enrollment

Individuals interested in participating in the study will complete a brief phone interview (~10min) to determine their study eligibility. Those deemed eligible will be scheduled for a virtual study intake session conducted over a Mass General Brigham Zoom and will be randomized to either the experimental (HRVB + TAU) or control group (TAU only). On the study intake Zoom call, participants will be invited to provide informed consent using the REDCap e-Consent Module.

The consent form will include language indicating experimental group participants will be invited to participate in a focus group following the 8-week course of HRVB.

6. STUDY PROCEDURES

On the study intake Zoom call, after providing informed consent (~10min), participants will complete a series of questionnaires via a secure REDCap link provided in the Zoom chat-box (~45min). Following this, participants will be guided through the process of installing the TigerAware ecological momentary assessment app on their smartphone and instructed how to use it (~5min). Finally, for experimental group participants, the researcher will provide the study rationale and give brief instruction in paced breathing (~30min). Immediately following the intake call, the experimenter will arrange for a Lief device to be mailed to the participant by Lief Therapeutics, which will come with instructions for setting up the device and downloading the accompanying smartphone app.

To maximize ecological validity in this study, the same HRVB phone coaching offered to regular Lief subscribers will be available to the experimental group participants. The Lief coaches are experts in HRVB and can help with any technical issues with the equipment or queries pertaining to the participant's HRVB practice. Coaches will reach out to study participants to schedule a 20-minute onboarding call when the Lief equipment is ordered. During the orientation call, the Lief coach will cover the following topics:

- Why HRV matters for your mental and physical health
- How Lief's HRV tracking and biofeedback training will help you achieve your health and wellness goals

- How to do a Downtime practice (a.k.a. HRV biofeedback exercise)
- Understanding how Lief's autodosing program works
- The coach's role: "*As your coach, I will support you as a sensemaker of your data to optimize your use of the Lief so we help you self-regulate your stress response more effectively"*
- Communication expectations: Mostly in the app chat box, I'll respond on weekdays. Schedule 20-minute calls every 2 weeks in the app so we can review your progress together.

Then, after experimental participants receive their device, they will have the option of communicating as often as they want with their coach in the Lief app's chat box. Coaches aim to respond within a business day (asynchronous communication). Participants will also have the option of scheduling 20min, *ad hoc* coaching sessions with one of Lief's coaches. Importantly, these HRVB phone coaching sessions are not psychotherapy, nor are they designed to replace psychotherapy, and Lief's coaches are trained to only offer support related to HRVB.

Throughout the 8-week study protocol, all study participants will have as needed access via phone and text to the study research coordinator, should issues with the ecological momentary assessment application arise, or the participant has any other questions or concerns. This will be a convenient channel through which participants can contact research staff for technical assistance, however, research staff may contact participants to check apps are functioning properly, for instance, in the event a participant has missed a lot of ecological momentary assessment surveys. We will use the MGB Cisco Jabber messaging app to create a unique study contact number at which the study research coordinator can be reached.

The heart rate variability biofeedback intervention
The HRVB equipment in this study includes a wearable ECG monitor (known as the Lief Smart Patch) and a smartphone app.

The Lief Smart Patch is a wearable, ECG-based heart rate monitor. It is attached to the body utilizing skin-safe ECG electrodes. ECG technology is known to be safe and carries no substantial risk. The Smart Patch senses stress and anxiety in real time based on HRV and breathing patterns, and then provides a breath-based heart rate variability biofeedback intervention. The Smart Patch collects heart rate, heart rate variability, and accelerometer data through continuous monitoring. These data are synced with the end-user's smartphone via Bluetooth Low Energy, then encrypted and sent through their wireless network to Lief's HIPAA-compliant server. This device does not collect data on geo-location, nor does it have any participant information stored on it. If a device is lost, there is no risk to participants of a privacy breach.

Experimental group participants will use the complementary Lief smartphone app to engage in the 8 weeks of HRVB. The Lief app is compatible with iOS and Android devices and provides a visual interface that supports HRVB practice. It also includes architecture that allows end-users to schedule *ad hoc* phone coaching sessions.

Focus groups
Experimental group participants (*N*= 10) will participate in 60-minute, audio-recorded focus groups moderated by the PI. There will be two groups of 5. These focus groups will gather feedback on participant interest in ambulatory HRVB, perceived benefits, and barriers to practice/device use.

Participant Compensation
To encourage study completion, participants (*N*= 120) will be compensated with an Advarra gift card loaded in installments.

The compensation breaks down as follows: Participants will be compensated $50 for completing the study intake/orientation and baseline questionnaire measures. They will also be compensated $100 for completing the ecological momentary assessment component of the study (defined as completing surveys every week of the 8-week study period), with a $100 bonus payment for achieving ≥90% ecological momentary assessment survey completion over the whole 8-week study period. Also, to motivate the return of ECG monitors and give the experimental group extra compensation for their additional work in the study, the experimental group will also receive a $100 bonus for return of study equipment. Participants who participate in the focus group will also be compensated $50.

The $50 for completing the study intake session will be provided immediately following the intake session. The remainder of the compensation will be electronically added to participants' Advarra gift card at the end of the 8-week study period.

Sending and Receiving Data
Lief Therapeutics will provide the PI Dr. David Eddie with the participants' physiology data, including heart rate variability, wear time, and paced-breathing practice time. This physiology data will be available for download from the Lief participant dashboard. The deidentified data file will be sent to the study email for direct download and saved to the study drive for analysis. Participant data that the study team cannot directly download will be retrieved by Lief Therapeutics and shared to the study team using a secure, MGB DropBox account.

Participant data will not be shared with Lief Therapeutics or TigerAware. Deidentified data will be shared with Co-I Dr. Noah Emery at Colorado State University in the form of datasets. Datasets will be shared using a secure, MGB DropBox account.

7. Risks and Discomforts

We believe there to be only minimal risks associated with this study. We will ensure proper confidentiality of information by training staff about the critical importance of confidentiality and providing study ID numbers for participants' study information. Identifying information will not be kept with collected assessment data. Research staff will be trained appropriately and undergo human research subjects protection training. Secure soft and hard data storage mechanisms will be in place (i.e., locked offices/suites, password-protected databases). Although we will reimburse subjects for their time and efforts, we do not believe the amounts to be coercive.

Out of necessity, we will provide Lief Therapeutics with experimental group participants' name, address, and phone number so equipment and phone coaching can be provided. This is a commensurate level of individual-level information Lief securely hold for thousands of subscribers. No additional participant information will be shared with Lief Therapeutics. Lief Therapeutics will not have access to participants' demographic, questionnaire, or ecological momentary assessment data.

The risk to participants in this study is relatively low because it does not involve invasive procedures or the administration of medication, and we will not be asking participants to modify their day-to-day behaviors in profound ways. Potential risks in the study are considered minimal and include, 1) potential discomfort related to completing questionnaires about sensitive topics such as psychological problems, and 2) potential breach of confidentiality and/or privacy.

Though potential risks of study participation are considered minimal, it is important to have participant protection plans in place. Participants will be informed they are free to withdraw from the study at any time. Also, we hope that any potential subjective discomfort from completing questionnaires will be minimized by assurances that participants can refuse to answer any question that they do not feel comfortable answering. In the event, however, that discomfort or distress do arise during any aspect of the laboratory visits, participants will receive support.

Participant names and contact information will be maintained in a secure recruitment/enrollment database in REDCap. Signed consent forms will be electronically stored on Mass General Brigham's REDCap e-Consent secure server.

All ecological momentary assessment data collected using the TigerAware app will be saved on TigerAware's encrypted, HIPPA compliant server, with copies of this data stored on Mass General Brigham's secure server in a designated study folder. No identifying participant information will be shared with TigerAware. Participants will only be identified by a unique study number in the TigerAware system, and not by their name. The TigerAware system does not require participant information such as an email address or phone number to function, nor does it require participants to sign an end-user license agreement.

In the event we encounter issues running the TigerAware app on a participant's smartphone, we will use REDCap's ecological momentary assessment feature as a backup. This feature works by linking REDCap with Twilio (an MGB approved texting app). Participants receive a text which links them to a REDCap survey through their smartphone's browser. Ecological momentary assessment collected this way will be stored with study questionnaire data also being collected through REDCap.

All ECG and HRVB digital practice records from the Lief app will be saved on Lief's encrypted, HIPPA compliant server, with copies of this data stored on Mass General Brigham's secure server in a designated study folder. Though Lief will need participants' name, mailing address, and phone number to send them equipment and provide phone coaching, research staff will not share participants' demographic, questionnaire, or ecological momentary assessment data with them.

In the event researchers observe a potentially serious cardiac arrythmia during post processing of ECG recordings, the participant will be notified via phone call by the study PI who will encourage them to consult with their doctor.

All study data will also be backed up on a Mass General Brigham issued, password protected, server and a desktop computer housed in secure office at the MGH Recovery Research Institute. Breach of confidentiality via final study datasets is highly unlikely because all study data will be identified with a numeric code, will contain no identifying information, and will be stored on HIPPA compliant servers.

All research staff at the MGH Recovery Research Institute are fully trained in relevant ethical principles and procedures, including maintaining confidentiality, and are certified by Collaborative Institutional Training Initiative (CITI) to conduct research with human subjects. During the study, we will notify officials, as mandated by law, if a participant reports intentions to harm himself/herself or others, or reports child or elder abuse. Participants will be informed of these limits to confidentiality during the consenting process. Serious adverse events will be reported to the MGH Institutional Review Board immediately by telephone and by written report within 24 hours of our receipt of information regarding the event.

8. Benefits

A potential participant benefit for the experimental group is improved substance use and affective outcomes. A potential participant benefit for both the experimental and control groups may be increased awareness of personal patterns in affect through the conduct of ecological momentary assessment.

There are also considerable benefits to society associated with this study. Substance problems carry a tremendous emotional, medical, interpersonal, and societal cost. The knowledge gained in this study may lead to the adoption of a novel SUD treatment tool that bridges gaps in existing treatment approaches. The minimal risks associated with this research are reasonable given the potential benefits of this study.

9. Statistical Analysis

Because this is a pilot study with limited power to detect statistical significance, we will focus on interpreting effect sizes to inform a subsequent R01 trial. We note however, certain design strengths that will allow us to maximize statistical power. For instance, in our regression models, rather than just looking at main effects of group, we will also assess Heart Rate Variability Biofeedback (HRVB) practice time as a continuous measure with controls scored as 0. Additionally, power to test day-level associations is boosted by the repeated measures design with up to 84 repeated, momentary assessments per participant.

Please note that we use the term “day-level” below to denote effects at the level of individual ecological momentary assessment (EMA) surveys. From this perspective we have up to 84 repeated, momentary assessments of affect and substance use.

Aim 1. Assess ambulatory HRVB’s uptake by individuals with SUD in terms of practice time, and perceived barriers to uptake based on qualitative participant feedback

We will explore ambulatory HRVB engagement using HRVB practice time (engagement with regular daily practice; engagement with unscheduled, in-the-moment practice). As a general benchmark of intervention uptake success that can be used to guide the subsequent R01 design, we will accept ≥50% engagement/adherence to scheduled practice (with consideration given to both number of days practiced, and time practiced each day). In-the-moment practice is harder to assess given we cannot know exactly when participants are experiencing increases/high levels of negative affect outside of each EMA survey, however, as a heuristic, we will accept ≥50% in-the-moment practice as indicative of engagement/adherence, based on the ratio of just-in-time practice prompts responded to vs. ignored, and the number of days participants engaged in in-the-moment HRVB practice.

We will also explore perceived barriers to ambulatory HRVB uptake based on qualitative participant feedback provided from the focus groups. Focus group recordings will be transcribed. We will then conduct a systematic qualitative analysis of the transcripts using approaches we have used previously to contextualize findings and offer insights into participants' experiences.

Aim 1 Power
Based on our previous research of a similar nature, we anticipate that engaging 10 participants in focus groups will allow for sufficient diversity of opinion to stimulate discussion and will provide ample time for each participant to share their perspective. We are confident that this sample size will give us the information we need to refine our intervention and research procedures for the subsequent R01.

Aim 2a. Test day-level effects of HRVB practice on affective states and substance use.
We will create indices of EMA recorded positive affect ([happiness + calm + energy] ÷ 3) and negative affect ([sadness + guilt + nervousness + stress + craving] ÷ 5) for each EMA survey (2 surveys per day with up to 84 surveys per participant), while also exploring craving scores as a stand-alone measure.

Using multilevel models where days (L1) are nested within persons (L2), we will explore the effects of day-level HRVB practice earlier in the day (i.e., lagged) on subsequent day-level negative affect (**Model 1**), craving (**Model 2**), positive affect (**Model 3**), and substance use (yes/no; **Model 4**), while also testing whether HRVB decouples the anticipated relationship of day-level negative affect (**Model 5**) and craving on subsequent substance use (**Model 6**).

In models 1-3 (multilevel linear regression models), the dependent variables will be day-level negative affect scores, day-level craving scores, and day-level positive affect scores, with lagged day-level minutes of scheduled practice, and lagged in-the-moment HRVB practice (with controls' HRVB practice coded as 0), and their interaction term (lagged scheduled practice × lagged in-the-moment practice) as the independent variables, controlling for age, sex, nicotine use (yes/no), medications known to affect the cardiovascular system (yes/no), and baseline past-month AOD use (percent days abstinent).

A priori, we anticipate that both greater daily scheduled HRVB practice and in-the-moment HRVB practice will predict lower subsequent day-level negative affect and craving, and that their interaction will indicate additive benefits of combining scheduled and in-the-moment practice. The relationship between positive affect and HRVB has not previously been explored, so we will treat this aspect of the analysis as exploratory. Our benchmark for preliminary demonstration of treatment benefit will be semi-partial R^2's for practice time of ≥ .10 (medium effect size).

Models 1-3

$$\textbf{Negative affect} = \text{day-level scheduled HRVB practice}_{t-1} + \text{day-level in-the-moment HRVB practice}_{t-1} + [\text{day-level scheduled HRVB practice}_{t-1} * \text{day-level in-the-moment HRVB practice}_{t-1}] + \text{age} + \text{sex} + \text{nicotine use} + \text{medications known to affect the cardiovascular system} + \text{baseline past-month AOD use} + \text{error}$$

$$\textbf{Craving} = \text{day-level scheduled HRVB practice}_{t-1} + \text{day-level in-the-moment HRVB practice}_{t-1} + [\text{day-level scheduled HRVB practice}_{t-1} * \text{day-level in-the-moment HRVB practice}_{t-1}] + \text{age} + \text{sex} + \text{nicotine use} + \text{medications}$$

known to affect the cardiovascular system + baseline past-month AOD use + error

Positive affect = *day-level scheduled HRVB practice* $_{t-1}$ + *day-level in-the-moment HRVB practice* $_{t-1}$ + [*day-level scheduled HRVB practice* $_{t-1}$ * *day-level in-the-moment HRVB practice* $_{t-1}$] + *age + sex + nicotine use + medications known to affect the cardiovascular system + baseline past-month AOD use + error*

In Model 4 (multilevel logistic regression), the dependent variable will be day-level substance use (yes/no), with lagged day-level minutes of scheduled, and lagged day-level minutes of in-the-moment HRVB practice (with controls' HRVB practice coded as 0), and their interaction term (scheduled practice × in-the-moment practice) as the independent variables, controlling age, sex, nicotine use (yes/no), medications known to affect the cardiovascular system (yes/no), and baseline past-month AOD use (percent days abstinent). We will also test this model with group as independent variable instead of HRVB practice.

In Models 5-6 (multilevel logistic regression), we will use a model building approach, where we will systematically increase model complexity in steps to sequentially examine hypotheses while maintaining a parsimonious model. Likelihood ratio tests will be used to examine the relative fit of nested models (i.e., the difference in –2 log-likelihood statistics between pairs of base and expanded models).

In Model 5, the dependent variable will be day-level substance use (yes/no), with combined lagged day-level scheduled and lagged in-the-moment HRVB practice (with controls' HRVB practice coded as 0), lagged day-level negative affect, and the lagged HRVB practice × lagged negative affect interaction term as the independent variables, controlling for age, sex, nicotine use (yes/no), medications known to affect the cardiovascular system (yes/no), and baseline past-month AOD use (percent days abstinent). We will also test this model with group as independent variable instead of HRVB practice.

In Model 6, lagged day-level craving will be added to Model 5. As with the previous model, the dependent variable will be day-level substance use (yes/no), with lagged day-level scheduled and lagged in-the-moment HRVB practice combined (with controls' HRVB practice coded as 0), lagged day-level negative affect, lagged day-level craving, and the lagged HRVB practice × lagged craving interaction term as the independent variables, controlling for age, sex, nicotine use (yes/no), medications known to affect the cardiovascular system (yes/no), and baseline past-month AOD use (percent days abstinent). We will also test this model with group as independent variable instead of HRVB practice.

We anticipate that greater HRVB practice and lower negative affect and craving will be associated with lower probability of substance use at the subsequent EMA survey, and that the HRVB practice × negative affect/craving interaction terms will indicate that HRVB practice mitigates the deleterious relationship between negative affect and craving, and subsequent substance use. McFadden's $R^2 \geq .10$ (medium effect size) will be our benchmark for preliminary demonstration of day-level treatment benefit.

Models 4-6

Substance use = *day-level scheduled HRVB practice* $_{t-1}$ + *day-level in-the-moment HRVB practice* $_{t-1}$ + [*day-level scheduled HRVB practice* $_{t-1}$ * *day-*

level in-the-moment HRVB practice $_{t-1}$] + age + sex + nicotine use + medications known to affect the cardiovascular system + baseline past-month AOD use + error

Substance use = *total day-level HRVB practice $_{t-1}$ + day-level negative affect $_{t-1}$ + [total day-level HRVB practice $_{t-1}$ * day-level negative affect $_{t-1}$] + age + sex + nicotine use + medications known to affect the cardiovascular system + baseline past-month AOD use + error*

Substance use = *total day-level HRVB practice $_{t-1}$ + day-level negative affect $_{t-1}$ + day-level craving $_{t-1}$ + [total day-level HRVB practice $_{t-1}$ * day-level negative affect $_{t-1}$] + [total day-level HRVB practice $_{t-1}$ * day-level craving $_{t-1}$] + age + sex + nicotine use + medications known to affect the cardiovascular system + baseline past-month AOD use + error*

Aim 2a Power
With *N*= 100, and 42 days of EMA monitoring with 2 self-reports per day, the multilevel models exploring day-level relationships between HRVB practice, affect, and substance use will include 8,300 clustered observations. Given 5% alpha and a substance use/HRVB practice association of *r*= 0.15, and assuming conditional independence, we will have >99% power to predict a main effect of HRVB practice in Models 1-6.

Aim 2b. Test the accumulative, person-level effects of scheduled daily HRVB practice vs. in-the-moment HRVB practice, vs. their interaction on substance use during the 8-week intervention period

To begin to tease out the aggregated effects of scheduled vs. in-the-moment HRVB practice on substance use, we will run a linear regression model with percent days abstinent (PDA) from alcohol and other drugs (AOD) over the 8-week study period as the dependent variable, with total aggregated scheduled HRVB practice time, total aggregated in-the-moment HRVB practice time, and their interaction term (scheduled practice × in-the-moment practice) as independent variables (with controls' HRVB practice coded as 0), controlling for age, sex, nicotine use (yes/no), medications known to affect the cardiovascular system (yes/no), and baseline past-month AOD use (percent days abstinent; **Model 7**). We will also run versions of this model testing a main effect of group, and number of in-the-moment practice sessions rather than aggregated in-the-moment HRVB practice time.

A priori, we anticipate that both greater accumulative scheduled HRVB practice, and accumulative in-the-moment HRVB practice will predict greater PDA, and importantly, that their interaction will indicate additional benefits of combining scheduled and in-the-moment practice. A semi-partial R^2 value for HRVB practice time ≥ .10 (medium effect size) will be our benchmark for preliminary demonstration of aggregate-level treatment benefit.

An ancillary aim of this study is to explore the effects of differing HRVB practice times on treatment outcomes. We will conduct a post hoc regions-of-significance analysis to explore the moderation effect of practice time on the relationship between PDA and HRVB practice. This analysis will consider the effect for several alternate cutoff scores representing the 10th, 20th, 30th, 40th and 50th percentiles of practice time.

Another ancillary aim is to garner a better understanding of when HRVB effects come on-board and how stable the effects are once established. To accomplish this, we will explore how the effect of HRVB on affective states and substance use vary over the trail using time-varying effects modeling (TVEM). TVEM estimates a non-parametric spline regression that flexibly estimates how the association between a predictor and outcome across continuous time (e.g., days). The series of regression coefficients produced by TVEM are presented graphically with 95% confidence intervals to demonstrate the magnitude and direction of the association between predictor and outcome across time. The P-spline technique, which automatically selects the best coefficient function through balancing tradeoffs between model fit and parsimony, will be used for all models.

Model #7

PDA = *total scheduled HRVB practice + total in-the-moment HRVB practice + [total scheduled HRVB practice * total in-the-moment HRVB practice] + age + sex + nicotine use + medications known to affect the cardiovascular system + baseline past-month AOD use + error*

Aim 2b Power

Though our emphasis will be on effect size interpretation rather than statistical significance, we note that with *N*= 100, 80% power, and a 5% alpha level, the detectible effect size is R^2= .10 (small effect size).

10. Monitoring and Quality Assurance

In an effort to meet the MGB policy for Data and Safety Monitoring, we have created a system for oversight of the project. Oversight of internal monitoring of the subjects' safety is conducted by the PI, Dr. David Eddie.

On a weekly basis, the PI and study staff will discuss the progress of the study, review data quality, recruitment, study retention and examine other factors that may affect the outcomes. We will review the rate of adverse events to determine any changes in participant risk. The investigators are available to meet outside of the weekly meetings, if necessary, due to concerns regarding a particular participant or any problems that may arise for participants.

Mandated reporting procedures will be followed according to Massachusetts state law in cases of abuse or neglect. Study staff will monitor and ensure validity and integrity of the data and adherence to the IRB-approved protocol. During meetings with research staff, consenting procedures, data collection, security, and entry will be reviewed by the PI. Furthermore, study staff will conduct periodic, random checks on all consent forms and procedures. Any adverse events that are observed and/or reported by study staff will immediately be reported to Dr. Eddie. Serious adverse events are reported to the MGH IRB immediately by telephone and by written report within 24 hours of our receipt of information regarding the event.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

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