STATISTICAL ANALYSIS PLAN

Impact of Community-Based Biofeedback Program on Drug Use and Mental Health Among People Experiencing Homelessness

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1. Study Specific Aims and Hypotheses

Specific Aims, Study Objectives, and Research Hypotheses

This one-year pilot study will build on our COVID-19 CRAFT study in which we initiated our final COVID-19 Phase II Survey of 100 PEH beginning in April 2021 (IRB 2021-6426); wherein we will be recruiting PEH, 50 of whom were diagnosed with COVID-19 and 50 which were never tested or tested negative for COVID-19. This ongoing study aims to assess the impact of COVID-19 on PEH as it relates to worsening mental health and substance use, as well as keeping safe during the COVID-19 pandemic, and COVID-19 vaccination completion. This sample will nicely feed into our proposed HRV-BF study, in which we plan to re-enroll up to 50 homeless adults who meet eligibility criteria, and are randomized into a HRV-BF intervention (n=25) versus an attention control group (n=25). Interested participants will be randomized into one of two groups, as mentioned above, after informed consent is administered. After that, the HRV-BF baseline questionnaire will be completed. These participants will also be stratified based on the following criteria 1) determined as infected with COVID-19 vs not infected; 2) high, moderate and low/no depression and 3) high, moderate and low/no levels of substance use. Prior to the intervention, we formed a Community Advisory Board (CAB) of 8 members from the COVID-19 study, 4 were COVID-19 recovered PEH and 4 not yet infected or not tested. The goal was to assess the feasibility and acceptability of the HRV-BF program. Results of this CAB revealed an excited group of PEH who were very interested in participating in the future study,and provided insight into how it can best be delivered so as to enhance recruitment and retention of the sample. Our proposal will be the first to pilot test an HRV-BF intervention focused on improving anxiety, stress, depression, and substance use among homeless and unstably housed PEH who have a history of alcohol and/or drug use as well as anxiety and depression during the COVID-19 pandemic. We plan to pilot test the 8-week HRV-BF intervention, utilizing our innovative RN/CHW model of care to 50 homeless adults. We will randomize the PEH into the 8-week HRV-BF (n=25) versus an attention control group (n=25), with follow-up survey at the 8-week period. PEH will be stratified according to a) COVID-19 infection versus COVID-19 infection naïve participants; 2) high, moderate, and low/no depression; and c) high, moderate and low/no self-reported levels of substance use. Specific Aim: Enroll PEH (N=50) and randomize into an HRV-BF intervention (n=25) versus a control group (n=25) to assess change in anxiety, stress, depression, HRV-BF, substance use and salivary cortisol levels from baseline to 8 week follow-up. Ho2a: Participants enrolled in the HRV-BF program will report significantly greater reductions in measures of anxiety, stress, and depression at 8-week follow-up as compared to the control group. Ho2b: Participants enrolled in the HRV-BF program will demonstrate significantly greater increases in HRV-BF indices at 8-week follow-up as compared to the control group. Ho2c: Participants enrolled in the HRV-BF program will demonstrate significantly greater decreases in drug and/or alcohol use at 8-week follow-up as compared to the control group. Ho2d: Participants enrolled in the HRV-BF program will show decreases in salivary cortisol, a known biomarker of stress, before and after each weekly session, and more normative levels of salivary cortisol at 8-week follow up as compared to the control group.

2. Rationale and Background Information

Scientific Rationale and Gaps in Current Knowledge

PEH are at high risk for COVID-19 as they experience higher rates of chronic diseases as compared with non-homeless populations. In Los Angeles (LA), there are 20.1 new cases per 100,000 people daily and over 1.2 million confirmed COVID-19 cases. Skid Row-Los Angeles is a critical COVID-19 epicenter as it hosts thousands of PEH living on the streets, hotels, and tents. Recent data from our qualitative study has revealed that stay-at-home orders have limited social services for these vulnerable groups, resulting in closed shelter doors and social isolation,

which has resulted in increased anxiety, stress, and depression, greater feelings of isolation and loneliness, and greater use of drugs and alcohol. This is concerning as there are large numbers of PEH who are underrepresented minorities; a subgroup experiencing the greatest mortality among COVID-19 infected Californians. It is projected that PEH will experience a 40% peak COVID-19 infection rate with 30% of COVID-19 positive people in the Intensive Care Unit. There is also concern that during COVID-19, both reduction of drug treatment services and increased stress due to economic conditions and social isolation may drive homeless adults to resume substance use. The need for cost-effective strategies that will target anxiety, stress, depression, and substance use, and that are partially delivered remotely, is of timely importance. One promising intervention, Biofeedback (BF) has been found to reduce self-reported depression among adult clinic patients, as well as reduce depression and substance use among residents of a substance abuse treatment program. BF is a process by which an individual's physiological processes and markers, such as heart rate, heart rate variability (HRV), respiration, muscle tension, surface temperature, and/or sweat (i.e., measures of sympathetic nervous system activation) are measured and "fed" back to the individual on a computer screen 19. Heart Rate Variability- Biofeedback (HRV-BF) is a form of cardiorespiratory biofeedback, wherein a client is given real-time heart rate data during guided slowed breathing in order to maximize respiratory sinus arrhythmia, producing a state of calm alertness. HRV-BF aims to maximize HRV, thereby modulating the transient or sustained elevations in sympathetic tone and reduction in parasympathetic activity observed in response to stress and negative emotions. Given the stressors experienced daily by PEH, we plan also to measure the potential modulation of the stress response by HRV-BF. Stressful situations produce remarkable cortisol secretion in most of the population. Cortisol secretion promotes an acute stress response as well as arousal, vigilance, and attentional focus. High levels of stress induced cortisol can also have serious adverse effects on physical health. As a biomarker for acute stress, and an indicator of HPA Axis adaptation to stress, salivary cortisol will be measured weekly in this pilot study.

Relevant Preliminary Research Data

Qualitative findings of 21 homeless adults and 10 health and social service providers revealed that COVID-19 has had a serious impact on closure of services in Skid Row. Furthermore, there is a high level of anxiety among both PEH and health and social service providers. Thus, PEH are staying isolated and afraid to seek what little services exist, while providers are not getting out into the community to provide services as they would like. Participants have also reported seeing more PEH dying on the streets from both untreated chronic disease as well as increased overdose deaths. Information about changes in substance use has been evolving. In addition, PEH who live on the street have informed the investigators that some drugs such a methamphetamine has been harder to come by and fentanyl has been more available and is more addictive and harmful. Thus, while it has become cheaper to purchase and available, the PEH who engages in this drug, becomes addicted much more quickly. Dr. Lee is currently studying the effect of a remote HRV-BF intervention delivered via telemedicine to frontline healthcare workers on their levels of stress, anxiety, and depression, compared to in-person biofeedback. While there are no findings yet, preliminary data from an employee wellness initiative of the SSIHI's Employee Well-Being Initiative shows the promise of remote BF. More than 270 participants have taken part in remote BF sessions, with 90% reporting overall benefit. Also in planning stages is a study using HRV-BF as a cardiac rehabilitation tool among an inpatient population hospitalized immediately following myocardial infarction.

3. Study Design and Endpoint Classifications

Study Outcome Variables and Predictors

Primary Outcomes Variables:

Impact of COVID-19 on Psychological Factors, HRV-BF and drug and alcohol use

- Psychological Factors: anxiety, stress, and depression will be measured as follows: Mental Health will be assessed by the MHI-5 which has well-demonstrated reliability for detecting psychological disorders. Depression will be assessed by the PHQ-9. Depression and Anxiety (GAD-7), Trauma, Coping, Loneliness, and PCL-C for PTSD Scale will be administered which will quantify stress and anxiety levels. All measures will be reassessed at 8-week follow-up.
- HRV-BF Indices: HRV measures will be assessed using photoplethysmography device.
- Drug and Alcohol Use will be assessed by the TCU Drug Screen.

Predictors:
Demographic Factors include age, race/ethnicity, history of substance use, personal health and travel history, known or suspected exposures to COVID-19, and type of work performed; county of origin, literacy level, hepatitis status, HIV, and history of mental illness.

Clinical Trial Design and Randomization Scheme

With the CAB session findings integrated into our planned intervention, we will conduct a randomized control pilot study, built upon our current COVID-19 CRAFT Survey of 100 PEH (IRB 2021-6426); wherein we are recruiting PEH, 50 of whom were diagnosed with COVID-19 and 50 which were never tested or tested negative for COVID-19. In the CRAFT study, we aim to assess the impact of COVID-19 on PEH as it relates to worsening mental health and substance use, as well as keeping safe during the COVID-19 pandemic, and COVID-19 vaccination completion. This sample will nicely feed into our proposed HRV-BF study, in which we plan to re-enroll up to 50 homeless adults who meet eligibility criteria, and are randomized into a HRV-BF intervention (n=25) versus an attention control group (n=25). Interested participants will be randomized into one of two groups, after informed consent is administered. After the consenting process is completed, the HRV-BF baseline questionnaire will be administered by trained research staff. These participants will also be stratified based on: 1) determined to be infected with COVID-19 vs not infected; 2) high, moderate and low/no depression and 3) high, moderate and low/no levels of substance use.

Definitions of Study Endpoints and Evaluation Criteria

Primary Outcomes:
1. Impact of HRV-BF intervention on change in anxiety, stress, and depression.
2. Impact of HRV-BF intervention on increases in HRV-BF indices
3. Impact of the HRV-BF intervention on decreases in drug and/or alcohol use.

4. Statistical Analysis Plan (SAP) Specifications

Statistical Methods for Specific Aims and Hypotheses

Demographic, behavioral, and clinical characteristics will be examined during the final two months, and frequency distributions produced. Measures of central tendency and variance will be estimated on each continuous measure; proportions will be estimated for categorical variables and graphical displays produced. We will perform multiple linear regression (LR) analysis by determining the associations between intervention group (1 = HRV-BF; 0 = attention control) and each dependent variable: anxiety, stress, depression, alcohol use score, drug use score, and HRV indices. History of COVID-19 will be included as covariate for each model. R v4.0.2 will be used for all analyses. Given that this is a pilot study, we will perform statistical tests using a one-tailed alpha-level of 0.05. Positive findings will be verified in a future validation study.

Statistical Methods for Primary Outcomes and Endpoints

We will perform descriptive analysis first, followed by multiple linear regression (LR) analysis by determining the associations between intervention group (1 = HRV-BF; 0 = attention control) and each dependent variable: anxiety, stress, depression, alcohol use score, drug use score, and HRV indices. History of COVID-19 will be included as covariate for each model. R v4.0.2 will be used for all analyses. Positive findings will be verified in a future validation study.

Sample Size and Power Determination Justification

Sample Size and Power. Given that this is a pilot study, we will perform statistical tests using a one-tailed alpha-level of 0.05

5. Chronological Research Procedures and Protocols

Chronological Clinical and Treatment Plan Description

Clinical Treatment and Recruitment Plan

50 homeless adults, 25 of whom who have recovered from COVID-19 infection versus 25 not diagnosed with COVID-19 and previously enrolled in the COVID-19 CRAFT Study. The prior participants (or continuing to be enrolled CRAFT participants) will be informed of the HRV-BF study by phone or in person or by IRB-approved flyer and interest in participating in the proposed study upon completion of the CRAFT survey. These homeless adults will be recruited from homeless shelters and streets in Skid Row. All sites are geographically close to each other and are homogeneous in terms of the demographics of the population treated. The research team will coordinate the recruitment effort. If the person wishes to participate and is eligible based on the COVID-19 CRAFT study, they will be provided more details and randomized to one of the two groups. The CHW will then complete the respective group's informed consent at the primary research site office or other isolated space at The Union Rescue Mission; or other participating institutions (see Appendix A); or homeless participants' current hangout location while maintaining privacy (e.g., hotels, streets, park, or tent etc). Participants interested in the study will be provided with the following information:

- Recruitment flyer
- Randomization
- Informed Consent
- 30-minute Baseline questionnaire
- 8-weekly Education sessions
- 30 minutes 2-month follow up

Randomization Scheme

are identified, and eligibility is confirmed, we will randomly allocate participants to one of the two study arms (HRV-BF or Attention Control) in a 1:1 ratio, stratified by COVID-19 status, gender, levels of depression and substance use. The project biostatistician will create a randomization table prior to study initiation. This table will be uploaded to the RedCAP Randomization Module, which will then be used for the assignment of participants to one of the two study arms.

Participant Photograph Policy

with recalling the identities of the research participants to track them for their follow-up assessment, the research staff would like to take photographs of the participants after the initial visit on RedCap. This photograph will be viewed only by the IRB-approved research staff and won’t be shown to anyone else outside of the research study. At the end of informed consent,

the participant will be given the option to accept or decline the photograph without affecting their participation in the study. This photograph will be destroyed at the end of this study.

Locator Guide
will ask for information guided by a detailed locator guide to eligible participants to assure follow-up. The Locator Guide will record name and address of the participant, driver's license number, hangout locations, etc for ongoing tracking purposes for participants who have missed doses or follow-ups.

Baseline Questionnaire Specifications
will administer a 30-minute electronic questionnaire on RedCap. The questionnaire will ask questions about the participant's socio-demographics (e.g., age, birth date, gender, race/ethnicity, education, religion, employment, relationship status, country of birth, shelter stability, social support, homelessness and substance use, psychological factors. In addition, they will complete structured instruments on drug use (TCU Screener), Depression (PHQ9), GAD-7 (General Anxiety Disorder-7, Mental Health, Trauma, Coping, Loneliness, and PCL-C for PTSD. In addition, an 8-minute assessment of baseline HRV indices.

Baseline Urinalysis Protocol
to provide a urine sample at baseline to test for recent drug use. The urine sample will be monitored with a temperature strip and will be analyzed for several street drugs (e.g., marijuana, heroin, etc.). The testing will be used to see the effectiveness of the intervention on reduction of drug use

Study Arm 1: Heart Rate Variability-Biofeedback (HRV-BF) Intervention (n=25)
A team of 3 CHWs and a research RN will deliver all components of the program. Recruitment will be continuous: each CHW may be assigned up to 4-5 participants every 2 months until target sample size (n=25 for intervention group) is achieved. HRV-BF Intervention will be delivered once weekly by the CHW. Each week, the participant will view an approximately 10-minute video on a tablet device carried by the CHW and complete an additional 10-minute biofeedback practice using either an audio recording/app provided by the CHW. Participants will also be asked to complete daily practices, for 10 minutes, twice a day, to reinforce topics and skills taught in videos. Practices logged by the participant will be collected. Case Management Resources: These 8 weekly sessions will include the following elements described below (please see intervention content attachment for details): (Please see in attachments)

Study Arm 2: Attention Control Health Promotion (n=25)
will receive weekly visits by the CHW for 20 minutes to discuss several chronic health conditions that are highly prevalent among PEH and for which PEH have expressed an interest in knowing how to mitigate or prevent. These include high blood pressure, diabetes, arthritis, and high cholesterol. Attention Control Health Promotion Sessions: These sessions (8) will include the following elements described below (please see intervention content attachment for details): Module 1: Orientation Module 2: Basics of High Blood Pressure. Module 3: Basics of High Blood Pressure – Continued Module 4: Basics of Diabetes Module 5: Basics of Diabetes - Continued Module 6: Basics of Arthritis Module 7: Basics of High Cholesterol Module 8: Basics of High Cholesterol - Continued.

Heart Rate Variability (HRV) Measurements
The research staff will take a few measurements of participants' heart rate variability on HeartMath EmWave Pro Plus. These will be repeated at the end of the study in 8 weeks. After

a profile is created on EmWave Pro Plus software application using participant's Study ID #, a clean sensor will be clipped to participant's ear. Three brief assessments will be completed as follows:

- Resting HRV assessment (5 min) will be measured and the participants will be asked to remain seated quietly as still as possible without being uncomfortable, as if waiting for the bus, no chewing of gum, or reading magazines.
- Stress Prep: (3 min): Participants will be asked to prepare themselves mentally and emotionally for an important upcoming event or activity by focusing their attention in the center of your chest. They will then be instructed to try and activate and experience a positive feeling, such as care or appreciation for someone or some special place.
- 1 minute deep breathing assessment: Participants will be asked to follow the instructions in the emWave Pro Plus for this assessment, which consists of breathing deeply yet comfortably at the pace shown on the screen (5 sec in / 5 sec out).

2-Month Follow-Up Questionnaires

will be contacted again at 2 -months (±14 days) follow ups to complete a follow-up questionnaire. If the research participant is unable to meet with the research staff in person, the participant will be contacted for their permission to complete the follow up over the telephone. The follow-up questionnaires will repeat the same questions as asked at baseline and will take up to 30 minutes each.

2-Month Follow-Up Urinalysis

to provide a urine sample at again at 2-months (±14 days) follow up to test for recent drug use. The urine sample will be monitored with a temperature strip and will be analyzed for several street drugs (e.g., marijuana, heroin, etc.). The testing will be used to see the effectiveness of the intervention on reduction of drug use.

Participant Compensation Details

$15 for the baseline, $10 per weekly session with 2 saliva samples for 8 weeks ($80) and $20 for the 2-month follow up completed.

Technology, Software, and Data Management Specifications

- Office 365 apps Use: We will use the Office 365 which includes email, OneDrive, Teams etc. for daily operational purposes. This is maintained by UCI Irvine Health Information services on a secured encrypted server and allows you to store PHI data. We will use these application to send and share data across approved team members through secured email or shared folders. We will share these folders with collaborators and the research assistants at UCLA.
- Zoom: Zoom will be used by the research team to go over the data analysis and periodic team meetings. The research team members will share their screen to discuss findings. In addition, research literature and manuscript development will be discussed. Accessing Zoom meeting will be by invitation only. An email invitation to the meeting and password will be required to enter the meeting. Zoom sessions are completely temporary; data will not be stored on Zoom.
- TheBox: TheBox will be used to share project files (i.e., outputs, in progress manuscripts, etc), along with upload password-protected, de-identified qualitative data from all the 1:1 interviews, which have coded names and locations. TheBox is an encrypted, UCLA secured cloud-based file sharing and storage service.

- REDCap (Research Electronic Data Capture) a web-based system and maintained by UCI Irvine Health Information services on a secured encrypted server will be used to collect and store all data.
- HeartMath EmWave Pro Plus: The device uses a medical grade photodetector (photoplethysmograph) sensor to detect and analyze heart rate. It consists of a sensor which clips to a finger or ear which allows real time heart rate data to be visualized on the accompanying HeartMath application on a computer or tablet device, which is downloaded from HeartMath. There is a USB connection between the sensor and the computer/tablet.