PROTOCOL TITLE:

BioWare to Enhance Treatment for Alcohol Use Disorder and Posttraumatic Stress Disorder

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

Alcohol use disorder (AUD) commonly co-occurs with posttraumatic stress disorder (PTSD), often resulting in physical health problems and social and occupational difficulties.[1-5] *Concurrent Treatment of PTSD and Substance Use Disorders using Prolonged Exposure* (COPE) is an efficacious, evidence-based intervention for comorbid AUD/PTSD.[6] COPE integrates two evidence-based therapies—Relapse Prevention for AUD[7] and Prolonged Exposure therapy for PTSD.[8] Randomized controlled trials (RCTs) of COPE demonstrate its efficacy in reducing alcohol use and PTSD symptoms among military veterans and civilians.[9-11] However, attrition rates of over 40% remain problematic in this population,[9-13] and technological aids may enhance treatment retention and clinical outcomes. The primary objective of this study is to evaluate an existing mobile telehealth system ("BioWare") with real-time collection of BAC and subjective craving in participants with comorbid AUD/PTSD who are enrolled in COPE. The current technology, created in partnership with a local business with experience developing cutting-edge mobile technology platforms for health care (Zeriscope), allows the therapist to virtually accompany patients during the in vivo exposure (IVE) component of COPE and provides audio/visual streaming along with collection of indicators of affective engagement (i.e., GSR, HR, subjective distress, subjective craving), which the therapist uses in real-time to modify the exercise to be more effective and personalized to each patient. We will determine feasibility and acceptability of this innovative telehealth system in the comorbid AUD/PTSD patient population. Exploratory analyses will examine potential indicators of treatment response.

Specific Aim 1: Determine feasibility and acceptability of the new, extended system in five participants enrolled in COPE for comorbid AUD/PTSD (i.e., assess ability to turn on/off the equipment in ≤ 5 minutes; assess perceptions of usability, comfort, and utility of the technology).

Exploratory Aim: Identify preliminary physiological and subjective indicators that may predict reductions in alcohol use and PTSD symptoms.

2.0 Background

AUD and PTSD are Prevalent and Commonly Co-occur. AUD is a common mental health disorder, with a lifetime prevalence of 29.1%.[14] AUD is the fourth leading cause of preventable death in the U.S. and responsible for approximately 88,000 deaths annually.[15-17] PTSD is also a common psychiatric condition, characterized by intrusive thoughts and nightmares and avoidance behaviors.[6] Lifetime prevalence of PTSD is 8-20%.[18,19] Individuals with comorbid AUD/PTSD demonstrate a more complicated clinical course and worse treatment outcomes, as compared to individuals with either disorder alone.[20-23] A series of problems are common among individuals with comorbid AUD/PTSD, including medical problems, HIV risk behavior, suicide, greater treatment utilization, and worse treatment outcomes.[1,4,23,24]

COPE for Comorbid AUD/PTSD. COPE is an efficacious, evidence-based treatment for comorbid AUD/PTSD. Multiple randomized controlled trials demonstrate efficacy of COPE with regard to significantly reducing alcohol and drug use and PTSD severity in patients with co-occurring substance use disorders and PTSD.[9,25-28] COPE has been identified by the Veterans Affairs (VA) as a gold standard of behavioral healthcare. COPE integrates Prolonged Exposure (PE)[8] for PTSD with Relapse Prevention (RP)[7] for alcohol and drug use disorders across 12 psychotherapy sessions. Major components of COPE include *imaginal exposure* (revisiting the trauma memory during therapy sessions) and *in vivo exposure (IVE)* (approaching avoided but objectively safe stimuli in the "real world" such as driving or going to the grocery store). Even though COPE is highly efficacious, it is limited by high drop-out rates and not every patient will respond to the treatment.[9-13] Thus, there is a substantial need to identify methods of strengthening treatment retention and outcome. One way of accomplishing this is by integrating technological aids into the IVE component of COPE treatment.

IVE Component of COPE. While the imaginal exposure component of treatment is completed during the therapy session, the IVE component is conducted outside of the therapy session, typically without any

observation or monitoring from the therapist. This approach has numerous shortcomings; some patients fail to attempt the exercises (e.g., given high avoidance symptoms), other patients attempt the exercises but are under- or over-engaged, and patients with AUD may attempt the exercise while under the influence of alcohol. All of these situations interfere with the learning/extinction process that is needed for a successful IVE. At present, providers are reliant upon patient self-report, which is subject to inaccuracies due to retrospective memory or survey bias, and patients with AUD may not disclose their alcohol use.[29] Thus, substantial gaps exist in our understanding of what occurs during IVE, and which physiological, behavioral, or contextual factors are predictive of treatment response. The study leverages recent advances in mobile telehealth technology to mitigate these shortcomings by enabling therapists to virtually monitor and modify, in real-time, IVEs based on patient-specific physiological and subjective data to optimize treatment engagement and maximize the therapeutic value of IVEs.

The Telehealth System. The study uses an existing telehealth system ("BioWare") to target IVEs during COPE. BioWare allows therapists to remotely connect via mobile audio/video capabilities with a patient in their real-world environment. BioWare goes beyond typical telehealth platforms. Physiological indicators of distress (e.g., heart rate [HR], galvanic skin response [GSR]) are objective indices of activation and extinction learning, and numerous studies show that greater activation and reactivity before and during PE therapy among PTSD patients is associated with improved treatment outcomes.[30-35] The system monitors physiological activation so that if a patient is under-engaged during an IVE, adjustments can be made in real-time to enhance extinction learning. It also collects subjective indices of distress. In the study, the system will be adapted for patients with comorbid AUD/PTSD by obtaining a blood alcohol concentration (BAC) reading of 0.00, indicating sobriety, before initiating the IVE to ensure the exercise is optimal. The new system will also collect subjective craving in real-time to further assess the IVE and associated treatment outcomes. This extended telehealth system will allow therapists to optimize IVEs during COPE to maximize their therapeutic impact. This new system may increase patients' confidence and ability to attempt and complete IVEs effectively (e.g., attempt exercises while sober, attain optimal activation, remain in the situation long enough), and this may improve the efficiency of COPE and reduce attrition.

4.0 Study Endpoints

Feasibility and acceptability of IB-PE. We will examine feasibility and acceptability of BioWare in five participants enrolled in COPE for comorbid AUD/PTSD (i.e., assess ability to turn on/off the equipment in $\leq$ 5 minutes; assess perceptions of usability, comfort, and utility of the technology) (see assessment below).

Reductions in Alcohol Use and PTSD severity. Will identify preliminary physiological and subjective indicators that may predict reductions in alcohol use and PTSD symptoms.

5.0 Inclusion and Exclusion Criteria/ Study Population

Initial eligibility screening will be conducted by the PI, Co-Is, Coordinator, or a trained Research Assistant by telephone or in person. If preliminary inclusion and exclusion criteria are met, staff will schedule an assessment appointment for the participant.

Inclusion criteria

1. Male or female; aged 18-70 years.
2. Able to provide written informed consent.
3. Meet DSM-5 diagnostic criteria for current moderate to severe alcohol use disorder (assessed via the MINI)
4. Meet DSM-5 diagnostic criteria for current PTSD as assessed by the CAPS-5.
5. Participants may also meet criteria for a mood disorder (except bipolar affective disorder, see Exclusion Criteria) or anxiety disorders. The inclusion of participants with affective and anxiety disorders is essential because of the marked frequency of the co-existence of mood and anxiety disorders among

patients with AUD and PTSD. Concurrent substance use disorders (e.g., cannabis) are acceptable provided alcohol is the participant's primary substance of choice.
6. Participants taking psychotropic medications will be required to be maintained on a stable dose for at least 4 weeks before study initiation.

Exclusion criteria

1. Meeting DSM-5 criteria for a history of or current psychotic or bipolar affective disorders, or with current suicidal or homicidal ideation and intent. Those participants will be referred clinically for services.
2. Participants with current suicidal or homicidal ideation and intent.
3. Participants on psychotropic medications which have been initiated during the past 4 weeks.
4. Acute alcohol withdrawal as indicated by CIWA-Ar scores >8.
5. Pregnancy or breastfeeding for people of childbearing potential.
6. Currently enrolled in evidence based behavioral treatment for AUD or PTSD. Attendance at therapeutic activities (e.g., Alcoholics Anonymous) other than study sessions will be closely monitored using the Treatment Services Review.
7. Participants with implanted electronic devices of any kind, including pacemakers, electronic infusion pumps, stimulators, defibrillators or similar.

Women and members of minority groups will be eligible for participation. Children under age 18 will not be eligible for participation. The rationale for this is that different current treatment recommendations differ for children versus adults with PTSD. No special classes of subjects, such as, pregnant women, prisoners, institutional individuals, or others will be recruited for this study.

6.0 Number of Subjects

5 participants will be enrolled.

7.0 Setting

Procedures will be conducted on the MUSC campus. Out-of-office IVE locations will vary based on subject's needs and will take place at the designated location decided on by the subject and study team. This may include private (e.g., watching videos or at home, walking around yard) or public spaces (e.g., going to the grocery store, going to a park), depending on the subject's needs. Our previous research using BioWare in a PTSD sample (substance use disorders were exclusionary) shows that this can be done safely and effectively. To further ensure safety, subject's location information will be collected at the start of each IVE. Subjects will be monitored throughout the exercise. Zeriscope is a local small business in Charleston, SC, that specializes in mobile technology platforms for health care. Zeriscope is partnering with the study team to provide BioWare equipment and technology support. Zeriscope will conduct the Virtual In-Service Appointment with study participants but no other research procedures will take place at Zeriscope.

8.0 Recruitment Methods

The primary recruitment site will be the National Crime Victims Research and Treatment Center (NCVC) at MUSC and community-based clinics. We will also place IRB-approved study flyers in prominent locations in MUSC and local mental health clinics, as well as advertisements on social networking sites (e.g., Facebook, Craigslist). Participants both in state and out of state may see our advertisements and will be invited to participate. If necessary, remote (in state and out of state) participation will be offered to participants in the proposed project to minimize burden and maximize engagement and retention. Remote implementation also enables us to enroll participants outside of our immediate geographic area (including rural and/or out of state clinics), exponentially expanding our recruitment potential. As a result of seeing an advertisement or talking with someone involved in their clinical care, prospective subjects will be encouraged to reach out to the study team to learn more about the study or complete an online or phone

screener. In addition, the study team may reach out to prospective subjects if participants from other trials have agreed to contact for future research.

HIPAA Waiver for Authorization for Research may be used. We will be using the waiver to enhance the efficiency of participant enrollment once a patient is referred to us or contacts us for screening. This waiver will allow us to prevent and avoid creating patient burden and prevents the patient from unnecessary time and effort that could be used for other appointments. We are requesting a HIPAA waiver to have the approval to view their medical record to ensure no obvious exclusionary criteria exist *before* we bring them in for a baseline visit (recent suicidality, homicidally, psychiatric inpatient stays or psychosis). This would be beneficial to the patient because we could determine quickly if the patient would not be a good fit for research and make a proper referral. This would also eliminate the burden of a baseline visit where the patient would otherwise be asked to discuss trauma history at length.

9.0 Consent Process

Prospective participants will either contact the study team to learn more about the trial and/or to complete an initial screening process. Alternately, the study team may contact prospective participants who have previously agreed to be contacted for research directly for screening. If prospective participants complete the initial pre-screen process, they will be invited to come to our research office for a baseline visit or complete the visit via telehealth. Potential participants will be given a full description of the study procedures and asked to read and sign (or electronically sign) an IRB-approved informed consent form before any study procedures or assessments are conducted. Informed consent will take place on the MUSC campus or via telehealth. Initial eligibility screening will be conducted by the PI, Co-Is, Coordinator, or a trained Research Assistant by telephone or in person. If preliminary inclusion and exclusion criteria are met, staff will schedule an assessment appointment for the participant. In a private room, participants will be provided with a description of the nature and requirements of study participation and asked to read and sign an IRB-approved consent form prior to beginning any study procedures. eConsent will be conducted through an IRB-approved platform, such as Doxy.Me or RedCap.

10.0 Study Design / Methods

General Procedures. Interested individuals will be screened by telephone or in person. Individuals who meet inclusion/exclusion criteria will be invited to come into the office or will schedule a telehealth appointment for a baseline assessment. Potential participants will be given a full description of the study and asked to read and sign an Institutional Review Board (IRB) approved informed consent form before any study procedures occur. During the baseline visit, participants will complete a breathalyzer, pregnancy test (for people of childbearing potential), a battery of self-report measures, and diagnostic interviews. All eligible and interested participants will then receive 12, 90-minute sessions of COPE therapy (described below). Ineligible participants will be referred clinically.

Virtual In-Service Appointment. All interested and eligible participants for this pilot study will be provided with a technology package (either at the office or via mail) that includes a complete Zeriscope technology system (i.e., small camera, Bluetooth earpiece with microphone, and discrete monitors to measure and record heart rate and skin conductance, and breathalyzer), training materials, device cleaning supplies and face masks. After receipt of the technology package, a virtual in-service call will be scheduled with Zeriscope to review the use and comfort of the equipment. During the in-service call a Zeriscope service team member will teach the participant how to turn on/off the equipment, place the equipment on their arm/hand, and use the equipment.

COPE Therapy. All participants will receive 12 weekly, 90-minute sessions of COPE. In COPE, patients receive psychoeducation pertaining to the interconnectedness of AUD and PTSD, and learn techniques to identify and manage cravings, cope with thoughts about drinking and negative affect, enhance problem solving skills, plan for high-risk situations, and utilize effective drink refusal skills. The PTSD treatment component of COPE reduces PTSD symptoms via PE, a highly efficacious treatment that includes

systematic confrontation of trauma-related stimuli via (a) repeated imaginal exposure to the trauma memory during sessions, and (b) repeated in vivo (in real life) exposure to avoided places or situations that remind the person of the trauma (e.g., crowded stores or restaurants). AUD skills are integrated within each therapy session. COPE sessions will be recorded for patients to listen to at home to complete imaginal exposure homework. Within and between sessions, patients record pre, peak, and post subjective units of distress (SUDS, 0-100) and craving (0-100) ratings when completing imaginal and in vivo homework exercises.

During session 1, the Study Therapist will provide the rationale for COPE, review trauma and alcohol/substance use history, and conduct breathing retraining. Session 2 will include review of common reactions to trauma and coping with cravings skills. Session 3 will include introduction of SUDS and craving, in vivo hierarchy development, instructions on how to use the BioWare system, and a brief in-session practice. During the in vivo hierarchy development, participants will work with the study therapist to identify stressful triggers, listing these from most stressful to least stressful. The most stressful situation will be listed at the top of the hierarchy. A large part of COPE therapy is safely exposing the participant to these individualized stressful situations (for example, going to a mall, walking in a crowded grocery store, visiting a park or engaging in a stressful activity, such as watching a suspenseful video clip). Part of the COPE therapy includes going to these stressful situations as "homework" each week. That is, participants will be asked to expose themselves to their identified stressful scenarios outside of the office. Specific to this study, participants will be asked to wear the apparatus during these exercises. The exercises will be audio and video recorded. Sessions 3-11 include in vivo "homework" review and planning for next in vivo assignments, imaginal exposure, processing, and substance use reduction skills. During session 12, the therapist and patient review treatment progress and discuss potential next steps depending on each patient's needs (e.g., couple's therapy, vocational counseling). All Study Therapists will have a master's or doctoral degree, complete a COPE training, and attend weekly supervision during the trial. Session checklists will be used for fidelity to the manual [36].

Part of the COPE protocol includes in vivo exposure exercises and participants will be asked to wear the apparatus during these exercises. The apparatus includes a heart rate monitor that will be affixed to the participant's arm with a band and a skin conductance monitor that consists of a "reader" that affixes to the wrist with two electrodes coming out of the "reader" that attach to the palm with gel pads. The exercises will be audio and video recorded. The in vivo exercises will be guided by either the Study Therapist or a clinical support team member. This role will be referred to as the 'IVE Coach.' The IVE Coach will lead the participant in the in vivo exercises. The IVE Coach will use actionable data during in vivo exposures (e.g., HR, GSR, subjective units of distress and subjective craving) to modify the assignments in real time. The IVE Coach will virtually accompany patients to one in vivo exposure per week. The IVE Coach will be in close communication with the rest of the clinical support team regarding the participant's in vivo exposure completion. Study Therapists will receive a system notification each time a patient completes an in vivo exposure, along with a summary report from that assignment (e.g., total time, $\bar{x}$ and peak GSR). These data may be used to objectively monitor treatment progress and discussed with the patient in the office (e.g., to highlight habituation within or between in vivo exposures).[37] Wifi availability will be considered in the selection of the locations for guided in vivo exposures. In the rare event that wifi signal is not present during a guided in vivo exposure, the participant and IVE Coach will work together to find an alternate solution (complete the in vivo exposure without wifi, and/or complete an additional guided in vivo exposure at another time and location, and/or reevaluate the in vivo hierarchy and make modifications to include locations with wifi). If equipment malfunctions at any point throughout the study, a replacement system will be provided to the participant. Zeriscope will be notified of equipment malfunctions.

While there will be some variability based on individual patients and specific in vivo activities, the patient and IVE Coach will use synchronous audio/video to communicate. Upon both the participant and the IVE Coach logging into the system, the IVE Coach will have the participant use the breathalyzer before

beginning the IVE exercise. The IVE Coach will establish that the patient's breathalyzer reading is 0.00 and will provide a brief (3 min) review of the instructions before the patient begins the in vivo exposure. In the case that a breathalyzer reading is not 0.00 but is equal to or below 0.03, the IVE Coach will instruct the patient to wait 5-10, drink some water, and then reassess with the breathalyzer. If the breathalyzer still does not read 0.00 or in cases where the initial reading is >0.03, the guided in vivo exercise will not be conducted and will be rescheduled to another time.

A baseline of subjective and physiological reactivity for each in vivo exposure will be established in the 3-mintues prior to beginning the in vivo exposure exercise. During the exercise, if the patient is optimally engaged, as demonstrated by increasing physiological (e.g., skin conductance, heart rate) and subjective (increase in distress/craving scores) indices, the IVE Coach will provide encouragement to continue but will not interrupt the patient. If the patient is not engaged (e.g., showing low/no increase in physiological and subjective indices of engagement, not following instructions, engaging in distraction behaviors), the IVE Coach will intervene and review the instructions, provide specific guidance to help the patient engage, and provide feedback until the patient is optimally engaged to maximize benefits. After the in vivo exposure, a brief (5 min) processing will occur. The IVE Coach will ask the patient how he/she thinks the exercise went, what was learned, and plan the next in vivo exposure. The IVE Coach will complete a check-out form documenting how the exercise went and will communicate this with the clinical support team.

Telehealth: Participants in this research study may choose to complete informed consent/baseline appointment, study visits and therapy sessions via home-based telehealth (HBT) care (i.e., service delivery to patients in their homes using consumer-friendly, video-conferencing technology) which may likely enhance retention by directly circumventing financial and transportation barriers associated with traveling to MUSC for in-person sessions. HBT sessions will be delivered via standard desk, laptop computer, tablet, or smartphone running MUSC approved applications.

Assessments.

Primary Outcomes and Assessments. Primary outcomes include: (1) feasibility of the technology in this patient population, measured by participants being able to turn on/off the equipment in ≤5 minutes, and (2) acceptability of the technology, assessed with the System Usability Scale (SUS). See **Table 1** for additional measures. The instruments selected are standardized, have good psychometric properties, and are widely used.

Table 1. Assessment Instruments and Timeline			
Instrument Name	**Purpose/Domain**	**BL**	**Session 1-12**
Informed Consent	Obtain informed consent	X	
Breathalyzer	Assess BAC	X	X
Urine Pregnancy Test (for people of childbearing potential)	Assess pregnancy	X	
Demographics Form	Characterize sample	X	
Technology Proficiency Screen	Assess comfort with technology use	X	
BioWare Use/Return Equipment Consent	Collect consent from participant to require Zeriscope BioWare equipment	X	
Concomitant Medications Form	Assess medications	X	
Quick Structured Clinical Interview for DSM-5: Quick SCID-5	DSM-5 psychiatric disorders	X	
Clinician Administered PTSD Scale: CAPS-5	PTSD symptom severity (clinician-rated)	X	12
Life Events Checklist: LEC	Trauma Exposure	X	
PTSD Checklist: PCL-5	PTSD symptom severity (self-report)	X	X
Beck Depression Inventory: BDI-II	Depression symptom severity (self-report)	X	X
Columbia Suicide Risk (CSSRS)	Assess suicidality (only for participants who score >=1 on Item 9 of BDI-II)	X	
Clinical Institute Withdrawal Assessment: CIWA	Assess alcohol withdrawal	X	
Timeline Followback: TLFB	Quantity/frequency of alcohol	X	X
Alcohol Use Disorder Identification Test: AUDIT	Alcohol use problem severity	X	12
Treatment Services Review	Assess treatments participants are currently enrolled in	X	X
Turn On/Off System	Feasibility of system use		3
System Usability Scale: SUS – Patient Version	Acceptability; usability		6, 12
System Usability Scale: SUS – Therapist/Coach Version	Acceptability; usability		12
Telehealth Usability Questionnaire: TUQ	Usability of telehealth implementation		6, 12
In Vivo Exposures: IVEs	Physiological and subjective indices of engagement (HR, GSR, distress, craving)		3-11
Use of system survey	Feasibility		3-11
Post-exposure survey	Comfort and system usability		3-11
Client Satisfaction Questionnaire-8: CSQ	Satisfaction with treatment		12
Helping Alliance Questionnaire: HAQ-II	Therapeutic alliance		12
Exit Feedback survey	Collect general feedback on technology system		12
Adverse Events	Monitor AEs and safety		X
Note. BL = baseline, HR = heart rate, GSR = galvanic skin response			

Subject Compensation. Subjects will receive $50 for the baseline appointment, $25 for the in-service appointment, $25 for each of the 12 visits, and $25 for each guided in vivo exposure session. The total compensation available is up to $600. Payment will be provided in Visa gift card or pre-paid debit card, called a ClinCard. Subjects will be compensated at the end of each visit by IRB-approved study personnel.

The ClinCard works like a bank debit card and it may be used to purchase goods or services everywhere Debit MasterCard is accepted as long as the balance available on the card is not exceeded. Participants will be given a ClinCard at the beginning of the study. Each time they receive payment for participation in this study, the money will be added to the card, as outlined in the payment schedule above. The ClinCard will come with information on how to use the card, a phone number to call to set a PIN and a phone number to call to check the card balance as well as the study staff contact information in the case that the ClinCard is lost or stolen.

11.0 Data Management

Overview. Research materials obtained from participants include self-report surveys and structured clinical interviews, and physiological and behavioral observation data. All data collection described in this protocol is collected specifically for the purposes of the research project. To maintain confidentiality, all digital and paper data collected will be numerically coded. Paper data will be kept in locked filing cabinets and digital files will be kept on password-protected computers within MUSC encrypted data server. No parties shall have access to these data aside from the PI and necessary research staff. A master list of participant names, study ID numbers, and contact information will be kept in a location separate from study materials within MUSC encrypted data server. Access to research records (paper and computerized) will be restricted to the project staff. Names will not be used on assessments or be available in the research laboratory. The investigators and all study personnel will sign a confidentiality agreement that no identifying information of specific individuals will appear in any internal reports or external documents (e.g., peer-reviewed publications, presentations). Research subjects' data will be entered in a computer database with only number codes for identifiers and will not identify study subjects by name.

General Statistical Analyses. All analyses will be performed on the intent-to-treat sample consisting of all subjects. Baseline clinical and demographic characteristics will be collected and descriptive statistics will be run in SPSS v. 25 (IBM, 2019). The hypotheses and statistical approaches are presented below.

Hypothesis 1: BioWare will be feasible, as evidenced by at least 80% of participants being able to turn on/off the equipment in ≤5 minutes.

Hypothesis 2: BioWare will be acceptable, as evidenced by participants having an average score of 35 or greater on the System Usability Scale. To test these hypotheses, we will run descriptive statistics to assess proportion of participants who turned on/off equipment in ≤5 minutes and calculate mean ratings on the posttreatment assessment of the System Usability Scale.

Exploratory analyses will identify preliminary physiological and subjective indicators that may predict reductions in alcohol use and PTSD symptoms. To determine if higher levels of physiological and subjective engagement predict positive treatment response, mean heart rate, skin conductance, subjective distress, and subjective craving during IVEs will be calculated according to previously published methods.[33,34,37] Separate mixed effects models will be used to analyze these variables as predictors of CAPS-5, PCL-5, TLFB, and AUDIT scores at session 12. Although we will not have a large enough sample size to draw strong conclusions from these data, this will allow us to identify data trends that can be examined further in larger, NIH-funded projects to refine the telehealth system.

Data Management and Capture. We plan to use REDCap (Research Electronic Data Capture) for data capture and management for self-report surveys and clinical interviews. REDCap is a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap provides secure, web-based flexible applications, including real time validation rules with automated data type and range checks at the time of entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The system allows the research team to create and engage respondents using a variety of notification methods.

REDCap data dictionaries can be distributed for reuse at multiple institutions. The underlying database is hosted in a secure data center at MUSC, a secure environment for data systems and servers on campus, and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including, user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption.

Data that will be collected during IVEs (i.e., physiological data, self-reported distress and craving, and video-recorded behavioral observation data), will be stored on Zeriscope's secure cloud-based system, which is HIPAA-compliant and designed to rapidly store quantitative and qualitative data from IVEs. Only IRB-approved research personnel will access these data. The Zeriscope-issued cell will collect participant

data through the data plan and participant data be uploaded to the Zeriscope cloud in real time. De-identified data are collected via hard wire (video), bluetooth (audio and sensor data) and transmitted to the phone and cached, then transmitted (via cellular data coverage) to Zeriscope and removed from the phone. In the event that the phone loses signal, data will be temporarily stored on the phone and then will resume upload to the cloud automatically once the phone is back in range. The database will be secure and backed up daily. The cell phone will require a PIN or ID number for access. Because data are not stored directly on the phone there is no risk of loss of confidentiality if the phone is lost or stolen. The patient interface is set up such that participants do not even have the capability to view their own data on the app. The cell phone will have cellular and data connectivity in order for the system to function properly. However, the phones will be kept relatively bare-bones and locked down so participants cannot use it for other purposes. Participants will be required to return the phone at the end of the treatment portion of the study. Approved study staff will be able to access and review these IVE data via a password-protected account from their secure computers.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

This Data and Safety Monitoring Plan (DSMP) has been developed in accordance with the National Institutes of Health (NIH) Office of Human Research Protection (OHRP) to assure the appropriate clinical safety monitoring of study subjects participating in this project.

Summary of the Protocol. The proposed Phase I project will test a mobile technological system to be integrated into COPE treatment for posttraumatic stress disorder (PTSD) and alcohol use disorder. The investigative team will evaluate the usability, acceptability, feasibility, and preliminary efficacy of the system in 5 participants with PTSD and alcohol use disorder (AUD). The primary outcomes of interest include (1) feasibility of the technology in this patient population, measured by participants being able to turn on/off the equipment in ≤5 minutes, and (2) acceptability of the technology, assessed with the System Usability Scale (SUS).

Trial Management. The study will be managed from the Addiction Sciences Division within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina (MUSC), College of Medicine, Charleston, SC.

Responsible Party. Dr. Jarnecke (PI) will be responsible for distinguishing between serious adverse events (SAEs) and non-serious adverse events (AEs), and determining initial study relatedness.

Data and Safety Monitoring Board (DSMB). We will create a DSMB to monitor overall participant safety, the rate and severity of adverse events, and the validity and integrity of the data. The panel will include 2 researchers with experience in treating patients with PTSD or AUD and a biostatistician. The board may be called at any point if needed for unexpected AEs, etc. Modifications will be made in the procedures and/or the protocol if necessary, based on the recommendations of the board. Confidentiality will be maintained during all phases of the study.

Adverse Events. An *Adverse Event (AE)* is defined as any unwanted change, physically, psychologically or behaviorally, that occurs in a study participant during the course of the study that may or may not be related to study participation. All AEs will be reviewed weekly by the PI, and annually by the DSMB and MUSC IRB. A *Serious Adverse Event (SAE)* is defined as an adverse event that has one of the following outcomes: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, OR requires intervention to prevent one of the above outcomes.

AE/Unanticipated Problem Follow-up. Unanticipated problems, potential AEs and SAEs will be identified during the study via self-report data, as well as weekly assessments and interviews. All unexpected AEs and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff and reviewed by the PI at the weekly study team meeting.

Risks of Study Participation. Risks of participation related to inconvenience, psychological discomfort and boredom, physical discomfort, and confidentiality are outlined in the Human Subjects Section. Well-established strategies to protect participants against risks are also outlined.

Safety Reporting. AEs are reportable to the local IRB if the AE is unexpected AND related or possibly related AND are serious or more prevalent than expected. The IRB definition of *unexpected* is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of *related* is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. SAEs will be reported within 48 hours of knowledge of the SAE. In accordance with the MUSC IRB, any deaths that occur during the study or 30 days post termination from the study will be reported within 24 hours, regardless of whether it is expected or unrelated. Follow-up of all unexpected and serious AEs will also be reported to the appropriate agencies. All AEs are reviewed weekly by the PI, and annually by the DSMB and IRB. An annual will include 1) confirmation of adherence to the DSMP, 2) a summary of any data and safety monitoring issues that have arisen since the previous report, 3) a description of any changes in the study protocol or DSMP that might possibly affect risk, and 4) all new and continuing IRB approvals.

AEs and SAEs occurring during the course of study will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. All research staff involved with AE reporting will receive training including identification, evaluation, documentation and reporting. All research staff will identify any potential AEs during the course of the study from self-report data and administration of assessments and interviews. This information will be provided to the PI, who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

When a reportable SAE is identified, research staff will initiate an SAE form, and the following individuals will be notified within 48 hours of knowledge of the SAE: study co-investigators, the MUSC IRB, and members of the DSMB, as appropriate. If complete information is not available when the initial 48-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for review by the PI.

Study Safety. Protocols for reported AEs and SAEs are outlined above. All unexpected AEs and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff. At the weekly team meetings (or before if urgent), the research staff will report any premonitory symptoms of clinical deterioration. Study procedures will follow the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to Dr. Jarnecke. All requests by participant's physicians and other medical providers will be referred directly to Dr. Jarnecke.

All participants will be provided with a list of community resources upon study completion. Individuals presenting at any time with serious mental or physical health symptoms will be referred clinically for treatment. In the unlikely event that a participant demonstrates clinical deterioration, he/she will be referred clinically. In the event that emergency evaluation or intervention is necessary, the participant will be escorted by a study staff member to the psychiatric walk-in clinic or emergency room. Psychiatric hospitalization is available for emergencies at any point in the study. For subjects participating via telehealth or located outside of our immediate geographical location, the study team will identify the subject's precise geographical location and local crisis and police department numbers at the start of the study visit with a telehealth locator form. In the case of acutely suicidal or distressed subjects participating

remotely, the study team will identify initiate a call with a local crisis line or police department to send emergency help to the participant.

Data Management and Analysis. A data analytic plan is outlined in the Statistical Analysis section. This study will examine the feasibility and acceptability of BioWare in the COPE patient population. The main outcome variables include at least 80% of participants being able to turn on/off the equipment in ≤5 minutes and the System Usability Scale. Post-hoc exploratory analyses will determine if higher levels of physiological and subjective engagement predict positive treatment response. Please see the Statistical Analysis and Power section for more details.

Quality Assurance and Confidentiality. Data quality will be monitored by random inspection of the completed forms by research staff and any irregularities or problems detected will be discussed with the PI. Project therapists will receive standardized training from the PI and Co-Is. Adherence to the manual will be monitored using session checklists and weekly supervision. If therapy drift is observed the therapists will be re-trained.

DSM Plan Administration. The PI will be primarily responsible for monitoring the study. The PI and a statistician will examine the outcomes database for missing data, unexpected distributions or responses, and outliers. A DSMB report will be filed with the IRB on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs and SAEs. We will report main outcome results at the end of the trial. In addition, all AEs will be reviewed weekly by Dr. Jarnecke, and annually by the DSMB and local IRB.

For any SAE, the appropriate IRB-approved SAE protocol specific reporting forms will be completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. If complete information is not available when the initial SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. Follow-up of all unexpected and serious AEs will be reported to all regulatory entities including the local IRB and DSMB, as appropriate. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization, or until the subject is no longer in the study.

Stopping Rules for Clinical Trials. The trial will be stopped under any of the following conditions: 1) there is clear evidence of harm; 2) there is no likelihood of demonstrating treatment benefit, or 3) there is overwhelming evidence of the benefit of treatment.

14.0 Withdrawal of Subjects

All participants will be screened thoroughly for eligibility following informed consent. The PI may discontinue participation at any time if a participant demonstrates or reports significant distress, presents a risk of harm to self or others, or is otherwise unable to complete the study. Participants may withdraw from participation at any time during the study procedure. Clinical referrals to community resources will be made available to all study participants.

15.0 Risks to Subjects

Inconvenience, Discomfort, and Boredom: Some participants may experience distress by questions pertaining to their trauma or their emotional functioning. All participants will be informed at the outset that the study is voluntary, and they may terminate participation at any point. Our past and ongoing research suggests that data collection using many of these measures can be conducted without undue psychological distress or exacerbation of symptoms. This experience includes substantial research with younger and older adults, active duty service members, military Veterans, rape victims, victims of other forms of violence (e.g., natural disasters, car accidents), and work on large-scale studies asking questions about similar topics with general population samples. Legal risks arise if individuals are homicidal or

suicidal and make these intentions known to project staff, who may then be required to notify authorities and the target of homicidal intent. These risks are outlined in the informed consent documents.

Some participants may experience a temporary increase in PTSD or AUD symptoms during the COPE treatment. This is normal, not unexpected, and not associated with negative treatment outcomes. Research by our group and others shows that the majority of patients undergoing COPE treatment do not experience an increase in symptoms, and that any increases in symptoms that do occur are mild-moderate, temporary, and not related to retention or end of treatment PTSD or AUD symptoms.

In the event that subjects experience psychological distress secondary to participation, they will be encouraged to contact the Principal Investigators. Dr. Jarnecke (PI) is a licensed clinical psychologist. Participants will be given contact information for Dr. Jarnecke at the time of consent, as well as resources for local and national 24-hour hotline numbers. In addition, participants will have access to urgent care services at MUSC. The research team is comprised of licensed clinical psychologists with extensive experience working with adults who have experienced significant life stressors and PTSD. If assessors or project staff believe that a participant is significantly distressed by participation, the PI will be notified and will contact the participant immediately to assess distress and assure participant safety. If called by a participant, the PI will attempt to address all participant concerns and will set up an alternate referral for clinical services outside the project if desired.

Physical Discomfort: Participants may experience some physical discomfort from wearing the device. The foam electrode gel may cause mild irritation to the palm, though the electrodes being used have a unique, patented pre-gelled adhesive side with non-irritation gel especially developed to prevent allergic reactions. The foam electrode is latex free and therefore suitable for every skin type. We will instruct participants how to appropriately wear the device and have them practice wearing it. We will also provide written and illustrated instructions for how to wear and use the device during in vivo exercises to ensure it is as comfortable as possible.

Confidentiality: All possible efforts to protect participants' privacy and confidentially will be made throughout the course of the study. Participants will be provided with a written informed consent document which specifies the risks and confidentiality protections and limits of study procedures.

Sources of Materials: Data will be in the form of structured clinical interviews, self-reported questionnaires and subjective units of distress scale (SUDS) and craving ratings, and physiological data that will be obtained specifically for research purposes. Access to research records will be limited, as they will be maintained in a locked cabinet in the project coordinator's locked office within MUSC. Only researchers working on this project will have access to the participants' data. The material will be specifically obtained for research purposes. Telehealth sessions will be conducted using only approved MUSC applications to maintain confidentiality. Data will be collected by trained study personnel under the direct supervision of Dr. Jarnecke (PI). Participants will be permitted all the time they need to ask questions and/or consult with family members. Participant will be fully informed of all aspects of the study before signing the informed consent and beginning any study procedures.

Adequacy of Protection against Risks

Recruitment and Informed Consent Procedures: Participants will be primarily recruited from the Medical University of South Carolina (MUSC). IRB-approved flyers and brochures describing the study and providing contact information will be placed in the PTSD, substance use, and mental health clinics at both hospitals. We will also post IRB-approved recruitment flyers in prominent locations in other MUSC hospital clinics (e.g., internal medicine, women's health, emergency department). We will additionally recruit from the general community via online and local media advertisements. The research team has used these methods successfully in previous and ongoing research studies to recruit participants with PTSD, AUD, and other psychiatric conditions.

The research team and all of the study staff have completed (or will complete upon hiring) the Miami Collaborative IRB Training Initiative (CITI) course and its associated tests in research ethics. Informed consent (IC) will be collected at the study research offices, in a private, interruption-free environment. The PIs, Co-Is, or a Study Coordinator will obtain IC. The IC form will outline: a) the sponsorship of the study; b) the nature, purpose and procedures of the study; c) the voluntary nature of participation (i.e., participation is not required; participation can be discontinued at any time); d) the duration of the study; e) potential risks and discomforts, as well as benefits of participation; f) that all information will be kept confidential subject to the provisions of the state and federal law; g) compensation; and h) alternative treatments. The IC form will specifically review the potential for psychological distress, and the risks associated with treatment that may occur as a result of study participation. The IC form will be explained to participants in easy-to-understand language, and participants will be instructed to read the form carefully prior to signing it. The IC form will include emergency contact information for the PIs. Any questions pertaining to the study or consent process will be answered fully. Potential participants will not be required to make a decision to participate at the initial contact, though that possibility will be available. If participants wish to discuss study participation with their family and/or significant others, they will be encouraged to do so. Participants will be informed that they can discontinue their participation in the study at any time and that this decision will not influence the care they receive at MUSC. Consent will be documented by the signature of the participant on the IC form, accompanied by the signature of the individual obtaining the consent. Participants will be given a copy of the informed consent to keep. Research staff will document the informed consent process in the medical record of the participant.

Confidentiality: Risks to confidentiality will be minimized by using initials and code identifiers. There will be no linkage between a participant's identity and their responses. There will be only one master list of participants (not linked to any participant responses) which will be kept locked separate from all data and will be available only to the PI, Co-Is and approved study personnel. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers in the Study Coordinator's office) so as to protect the confidentiality of participant information. Access to research records (paper and computerized) will be restricted to the project staff. Data from the from the out-of-office IVE assignments using the technology system (i.e., audio/visual recordings, heart rate level, and moisture and temperature of your skin) will be stored on Zeriscope's secure, HIPAA-compliant server. Data will be stored for one year following study completion on Zeriscope's servers to ensure proper export of data. Data is not saved locally to the Zeriscope-issued cell phone and participants cannot view their IVE data from the phone so there is no risk of loss of confidentiality if the phone is lost or stolen. MUSC personnel will be responsible for owning and analyzing the data. Our research staff are well trained in the confidential nature of research subjects' records. Research staff complete annual courses on confidentiality protection and most recently on HIPAA regulations. These procedures are highly effective in protecting confidentiality issues. Names will not be used on assessments or be available in the research laboratory. The investigators and all study personnel will sign a confidentiality agreement that no identifying information of specific individuals will appear in any internal reports or external documents (e.g., peer-reviewed publications, presentations). Participants' data will be entered in a computer database with only number codes for identifiers and will not identify study subjects by name or other identifiers (e.g., birth date). These procedures have proved highly effective in preventing breaches of confidentiality in our current and previous research studies.

Assessment Procedures: Risks associated with assessment and treatment include the possibility that participants might be upset by questions pertaining to trauma or their emotional functioning or talking about their trauma. The research team will closely monitor participants for any increase in distress at every treatment visit. PTSD, AUD, and depression symptoms will be monitored weekly using standardized measures (PCL-5, TLFB, BDI-II) in order to detect any symptom worsening requiring further evaluation. Additionally, participants will be advised to observe any signs of worsening PTSD, AUD, depression, and other symptoms, and to discuss these with the research team. All participants will be informed at the outset that they may terminate participation at any point. If a participant becomes upset in-between visits, they

will be encouraged to contact the Study Coordinator, their Study Therapist, and/or Dr. Jarnecke. If a participant needs or desires immediate attention, arrangements will be made for an appointment with an experienced mental health provider. The informed consent document provides direction to contact the study staff during office hours and/or the Emergency Room at any time for worsening of symptoms.

Our previous and ongoing PTSD and AUD research suggests that data collection using many of these measures can be conducted without undue psychological distress or exacerbation of symptoms among participants. This experience includes substantial research with younger and older adults, military service members, rape victims, victims of other forms of violence, and work on large-scale studies asking questions about similar topics with general population samples. In the event that participants experience extreme psychological distress secondary to participation, they will be encouraged to telephone the PI. In addition, they will have access to urgent care services at MUSC. The research team is comprised of licensed clinical psychologists with extensive experience working with adults who have experienced significant life stressors and addiction. If project staff believes that a participant is significantly distressed by participation, Dr. Jarnecke will be notified and will contact the participant immediately to assess distress and assure participant safety. If called by a participant, Dr. Jarnecke will attempt to address all participant concerns and will set up an alternate referral for counseling for those who desire it from outside the project. All participants will review, at the initiation of participation, an informed consent document which specifically reviews potential psychological distress from the assessments or COPE therapy as a potential outcome of participation. If necessary, they will be asked to complete a safety plan and agree to call the project staff or 911. However, if safety is in question in the minds of any project staff, the Mobile Crisis unit of Charleston County, which involves a team of police and psychiatric workers, or the EMS unit will be dispatched to the participant's home to assure safety. In our NIH-, VA- and DoD-funded clinical trials of PTSD and AUD treatment provision, we have not had any problems related to participation that could not be safely resolved with these methods.

Physical Discomfort: Participants will have an in-service with Zeriscope to introduce them to the equipment, instruct them how to appropriately wear the device and have them practice wearing it. We will also provide written and illustrated instructions for how to wear and use the device during in vivo exercises to ensure it is as comfortable as possible.

16.0 Potential Benefits to Subjects or Others

While there is no guarantee of specific benefit to participants in this study, the potential benefits include a thorough psychological assessment and referral to appropriate treatment services and community resources. Participants may also benefit from receiving access to an evidence-based behavioral treatment which may result in a reduction in aversive PTSD symptom severity, AUD, and symptoms of other mental health problems (e.g., depression, anxiety) and improvements in other areas of functioning (e.g., sleep, quality of life). Other study benefits include regular contact with research staff, access to assessment information pertaining to PTSD and AUD, and referral to treatments for associated problems. While these benefits may be considered minimal, we believe that they outweigh the minimal risk and burden incurred by participants. Participants will also enroll in a study that has the potential to enhance treatment for other patients with PTSD and AUD.

17.0 Sharing of Results with Subjects

Study data will not be shared with participants to maintain confidentiality.

18.0 Drugs or Devices

BioWare is not classified as Humanitarian Use Device (HUD) nor a FDA mobile medical application. BioWare will provided to participants in person or shipped to their residence. BioWare will then be stored in participants' homes over the course of their participation in the study. Proper use of the system will be reviewed with the participant during the virtual in-service appointment. The BioWare participant interface

system is protected with a pin number to ensure that only the participant can use it. The BioWare system does not store information locally on the equipment and is instead uploaded to a HIPAA-compliant cloud-based server. There is minimal risk associated with using the Zeriscope BioWare system.

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