Official Title: Using Wearable Technology to Develop Biomarker-Driven Intervention for Alcohol-Facilitated Intimate Partner Violence

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SPECIFIC AIMS

Alcohol use disorder (AUD) and acute alcohol intoxication are well-established precipitants of intimate partner violence (IPV)[1-7]. Approximately one third of U.S. adults experience IPV during their lifetimes[8,9], with costs that exceed $3.6 trillion in expenses[9-12]. The health and financial burden of alcohol-facilitated IPV is particularly malignant, resulting in increased risk of mortality, morbidity, and poor treatment outcomes[11,13-21]. Recent data also indicate that IPV negatively impacts AUD treatment[13,22-27] and increases risk of relapse[28-31]. While some promising outcomes from behavioral treatments for co-occurring AUD and IPV have emerged[29,32-35], findings are inconsistent and grow increasingly spurious following completion[23,30,36]. Although behavioral treatments targeting AUD and IPV are effective for some women and men, efficacy is commonly limited by high dropout rates, poor working alliance, and low readiness to change[37-40]. As a result, there is a critical and persistent need to develop dynamic treatment options to successfully reduce AUD and IPV concurrently.

Mitigating maladaptive physiological reactivity in the form of respiratory sinus arrhythmia measure of heart rate variability (HRV) is one promising pathway to achieve this goal. HRV is an autonomic biomarker of arousal relevant to AUD pathophysiology, alcohol consumption, and treatment outcomes[41-44]. HRV is also an emerging mechanism underlying alcohol-facilitated IPV. Specifically, the combination of acute alcohol intoxication and emotional distress disrupt the central autonomic network's ability to regulate behavior, cognition, and emotion adaptively during couple conflict. Data from our group and others suggest that in controlled laboratory settings, alcohol intoxication and IPV are associated with acute elevations in heart rate and reduced HRV[45-47]. For example, our team recently found that in a randomized controlled laboratory study using an alcohol administration paradigm, distressed violent couples demonstrated lower HRV compared to distressed non-violent couples (N=38) during intoxication and evocative partner stimuli compared to control conditions[48].

Growing evidence suggests that biofeedback interventions to modulate physiological, emotional, and behavioral stress responses are feasible, acceptable, and may reduce AUD symptoms such as craving to improve long-term AUD recovery[49-53]. Our team extended this literature by conducting an exploratory pilot study among participants who had perpetrated IPV (N=4), and found that HRV biofeedback (HRV-B) conducted once daily for 10 days outperformed progressive muscle relaxation to restore normalized HRV. Taken together, this emerging data suggests that remote, self-administered biofeedback interventions hold promise as a discreet, accessible and low cost standalone or adjunct treatment option for AUD patients with high risk behaviors such as IPV. However, HRV has not yet been investigated as a mechanism of alcohol-facilitated IPV in naturalistic settings. Bridging this gap in the existing literature is essential to translate these promising laboratory findings into biomarker-driven treatment options to address this urgent public health problem. Thus, the primary objective of the proposed project is to use wearable technology to develop proof-of-concept of HRV as a biomarker of alcohol-facilitated IPV in naturalistic settings. Our secondary objective is to examine the preliminary usability, feasibility, and acceptability of a remote, self-administered HRV-B intervention.

To accomplish these goals, we will enroll a sample of 50 couples (100 total participants) with AUD and IPV into a 28-day micro-longitudinal study. Participants will wear activity trackers equipped with continuous ambulatory physiological monitoring and geolocation. Ecological momentary assessment (EMA; 4 times daily plus optional event-triggered reports) of alcohol use, couple conflict including IPV, and affect will be completed via smartphone application for 28 days. During days 22-28, participants will also be prompted to complete a 10 minute self-administered HRV-B session at least once daily. Subjective usability, feasibility, and acceptability of HRV-B will be assessed. The following Specific Aims are proposed:

Specific Aim 1: Employ a wearable physiological monitoring platform in combination with EMA and geolocation to examine the proximal role of HRV in alcohol-facilitated IPV among couples in naturalistic settings.

Specific Aim 2: Conduct a non-randomized, open-label pilot study examining the usability, feasibility, and acceptability of a remote heart rate variability biofeedback (HRV-B) intervention to reduce alcohol-facilitated IPV.

We hypothesize that episodes of alcohol use and IPV will be characterized by lower HRV as compared to episodes when neither alcohol use nor IPV occurs. We also hypothesize that HRV-B will demonstrate usability, feasibility, and acceptability as evidenced by use at least once daily and positive self-reported feedback. This translational study will advance the mechanistic science in this area by examining the proximal role of HRV in alcohol-facilitated IPV in naturalistic settings. This study has the added benefit of utilizing discreet wearable technology and geolocation to refine and optimize the content, dose, and timing of HRV-B. Findings will facilitate

the development of urgently needed just-in-time interventions that are personalized, accessible, and dynamic. The investigative team has the unique expertise necessary to implement this innovative study, which has the potential to yield essential public health impact. Findings will directly inform the design of a randomized controlled trial testing the efficacy of HRV-B to reduce alcohol-facilitated IPV through R01 series funding.

RESEARCH STRATEGY

Overview. The objective of this study is to examine the proximal role of respiratory sinus arrhythmia measure of heart rate variability (HRV) in alcohol-facilitated intimate partner violence (IPV) in naturalistic settings. Our secondary objective is to examine the usability, feasibility, and acceptability of HRV biofeedback (HRV-B) self-administered remotely for seven days in a non-randomized, open-label fashion. Participants will be *50 couples (total N=100*) with AUD and IPV. We will accomplish this by using wearable technology and a mobile application to complete ecological momentary assessment, physiological monitoring, and geolocation for 28 days.

APPROACH

Overview. This 28-day micro-longitudinal study will examine 1) the proximal role of HRV in alcohol-facilitated IPV in naturalistic settings, and 2) preliminary usability, feasibility, and acceptability of HRV-B self-administered via smartphone for 7 days. We will employ a unique combination of EMA, ambulatory physiological monitoring, and geolocation enabled by smartphone and discreet wearable activity trackers.

Participants. Participants (*50 couples; total N=100 participants*; 50% women with AUD) ages *21*-70 years, any gender identity or sexual orientation, and located in any state in the United States. The primary inclusion criteria are that at least one partner within each dyad must: 1) meet DSM-V diagnostic criteria for current AUD (MINI-7[146]) and current alcohol use based on (TLFB[147]), and 2) report at least one instance of physical IPV in the past two years (assessed via the CTS-2[148]). Additional inclusion criteria: 3) Cognitive functioning sufficient to provide informed consent and participate accurately (≥ 26 on the Mini-Mental Status Exam [MMSE][149]), 4) married, cohabiting, or in a committed relationship for ≥ 6 months, and 5) maintenance of psychotropic medications on a stable dose for at least 4 weeks before study initiation (to minimize pharmacologic effects on HRV). Exclusion criteria: 1) History of or current psychotic, bipolar, or antisocial personality disorders, 2) moderate or severe drug use disorder (e.g., cannabis). Concurrent mild drug use disorders are acceptable because of the marked frequency of co-occurrence among individuals with AUD. Moderate or severe Nonalcoholic Substance Use Disorder is acceptable if there has been no current substance use in the last 1-2 months. Drug use will be measured (via urine drug screen, TLFB, and EMA) and controlled for in statistical analyses if needed. 3) Alcohol withdrawal as indicated by CIWA-Ar score >8, 4) current suicidal or homicidal ideation and intent, 5) serious cardiovascular conditions (e.g., *pacemaker, cardiac arrhythmia, hypertension) because the safety of HRV-B has not been established in these populations*, 6) use of medications such as lithium, methadone, alpha or beta blockers or cholinergic/ anticholinergic drugs likely to confound normative cardiovascular responding, 7) current neurologic conditions *(i.e., Parkinson's disease)* or history of traumatic brain injury, 8) severe and unilateral IPV in the past 6 months (for safety), 9) current pregnancy. Pregnancy may cause discrepancies in heart rate that are not attributable to the study intervention which may present a confound for resulting theoretical findings.

Recruitment. *We need to enroll 2-3 couples per month with AUD and recent IPV in order to meet our target recruitment goal*. We will receive clinician referrals from MUSC's Center for Drug and Alcohol Programs (CDAP) and community providers in any state in the United States. The PI and CO-Is will utilize new and existing relationships with colleagues for referrals in state and out of state.

In addition, we will post IRB approved recruitment flyers in other MUSC and community treatment clinics and catchment areas. The study team will receive all required approvals before posting flyers outside of MUSC. This may include asking permission from clinics, restaurants, or other community areas. Advertisements will be placed on the internet (e.g., Craigslist and SCresearch.org) and will target in state and out of state participants. Participants who refer others to the study will be compensated $10 per randomized referral, allowing us to reach a wider pool of potential participating couples including couples from the community with IPV and AUD, in addition to treatment-seeking couples with IPV and AUD. Further, participants from past MUSC research studies who have consented to be contacted for future research studies will be recruited via telephone screening and/or e-mails. These individuals will be referred to us via other MUSC researchers, or they may have indicated consent

to be contacted about future research studies within the research group. The research team has used these methods successfully to recruit patients to clinical and laboratory studies.

Chart review and EPIC lists will be used for recruitment to find potential participants that have been identified as struggling with alcohol use or diagnosed with Alcohol Use Disorder. The study team will use an IRB approved letter and script to inform identified individuals about our study.

Potential participants will be asked to complete an online screener. Potential participants may also be sent a recruitment email that includes details about the study (e.g., time requirement, basic inclusion criteria, compensation), a link to the IRB approved screener, and contact information for the research team will be included in the email. Potential participants will also be contacted via phone.

Setting. All procedures will be conducted on the MUSC campus. Procedures can also be conducted via telehealth. Since this is an observational study, participants will engage in research assessments in their natural environment.

Telehealth. We are equipped to conduct the full scope of this project remotely, enabling us to enroll participants outside of our immediate geographic area, and outside the state of South Carolina. Participants in this research study may choose to complete this study 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. Further, telehealth allows the study team to recruit and enroll participants who are located outside of the state of South Carolina (inside US). HBT sessions will be delivered via standard desk, laptop computer, tablet, or smartphone running MUSC approved applications. Participants who choose telehealth will be required to have their own computer, tablet, or smartphone; to complete the study sessions however, a cell phone containing the required application may be provided to MUSC participants for the duration of the study as needed. Participants must consent to the shipment and receipt of study supplies in order to complete the study via telehealth, including pregnancy test, breathalyzer test, study supplies, consent, materials for UDS, HIPAA, and other study documents when necessary. Study materials will be shipped overnight by research staff to participant's designated location at the agreed upon date using overnight shipping with contracted shipping company (FedEx, UPS).

Prior to the screening appointment the study team will mail any necessary study documents, pregnancy tests and alcohol saliva strips to test for pregnancy and recent alcohol use. The alcohol saliva strip must read white (indicative of 0.00 BAC to validate the consent and prior to completing any study procedures. Further, prior to proceeding, females will be asked to take a pregnancy test and must provide verbal confirmation of a negative pregnancy test prior to proceeding with the screening appointment. At each visit, in lieu of a Breathalyzer Test, an Alcohol Saliva Test will be used to measure blood alcohol concentration (BAC) for telehealth visits. In front of the camera, participants will open the one time use test strip, place strip on tongue for 10 seconds, then hold test strip and a color chart to the camera for a study team member to assess. Samples reading >0.01 g/dl will be considered positive. The pregnancy tests used in this study are designed for at-home use, come with clear and simple instructions. In very rare and highly unlikely circumstances where the participant is unfamiliar with how to provide a urine sample or take an at-home pregnancy test, study staff can provide further instructions on how to provide a urine sample, how use the dipstick to test, and to differentiate between a positive and negative result. Ability and willingness to perform an at-home pregnancy test is required for telehealth female participants.

All telehealth participants complete a participant locator form with study staff, that allows the study team to identify local emergency care facilities and contact information. Specifically, for out of state or remote participants, the study staff will compile a list of referrals and emergency contacts to provide to study participants ahead of enrollment.

Eligibility Assessment. Following preliminary phone screening, those who elect in-person participation will complete private written informed consent apart from their partner, a breathalyzer, urine drug screen, and baseline eligibility assessment (Table 1). Remote participants will be mailed a study packet including written telehealth policies, procedural telehealth instructions for meeting with research staff, UDS cup and saliva alcohol strips, and a hard copy of the informed consent form ahead of their baseline assessment. Electronic informed consent, eligibility interviews, and sample readings will take place via videoconferencing (via Doxy.me) with research staff. Research staff always establish contact information for safety and that the participant is able to participate with privacy from other household members before beginning. All participants will complete self-report surveys via RedCap. Remote participants will receive a RedCap link via email or text to complete their baseline surveys online on their home computer, tablet, or smartphone. Eligible remote participants who choose to enroll will be mailed written instructions regarding how to use study equipment and complete EMA surveys, an activity tracker and charger, mobile device (if needed), and written HRV-B breath pace training script based on published protocol[145]. All participants will receive HRV-B and EMA training via telehealth or in-person with research staff. Ineligible participants will be provided with community and treatment resources.

Table 1. Eligibility Screening and Baseline Assessment Measures

Instrument	Purpose	BSL	Exit	Daily
Breathalyzer Test	Screen for alcohol	X		
Urine Drug Test	Screen for drug use	X		
Pregnancy Test	Screen for pregnancy	X		
Breathalyzer Policy	Required document	X		
Participant Locator Form	Required document	X	X	
Participant Contact Form	Collect contact information	X		
Demographics Form	Collect demographics	X		
Participant History Form	Collect medical history and medications	X		
Adverse Events Form	Collect adverse Events		X	
EMA Morning Report	Collect daily substance use, partner conflict, mood and affect, device accessibility			X
EMA Random Report	Collect daily substance use, partner conflict, mood and affect, device accessibility			X
CIWA-Ar	Assess alcohol withdraw	X		
Mini Mental Status Exam (MMSE)[149]	Screen for cognitive deficits	X		
QuickSCID[146]	DSM-5 psychiatric disorders	X		
Traumatic Life Events Questionnaire (TLEQ)[170]	Assess trauma history	X		
Time Line Follow-Back[147]	Alcohol and drug use, IPV	X	X	
PTSD Checklist (PCL-5)[172]	Assess PTSD symptoms	X		
Beck Depression Inventory-II (BDI-II)[171]	Assess depression	X		
Alcohol Use Disorders Identification Test[150]	Alcohol problem severity	X		
Fagerstrom Test for Nicotine Dependence (FTND)[169]	Assess nicotine use	X		
Comprehensive Effects of Alcohol Questionnaire[151]	Alcohol expectancies	X		
Drinking Motives Questionnaire-Revised[152]	Drinking motives	X		
Revised Conflict Tactics Scale[148]	Intimate partner violence	X	X	
Dyadic Adjustment Scale-short form[153]	Relationship functioning	X	X	
State-Trait Anger Expression Inventory[154]	Trait anger	X		
Dissipation-Rumination Scale[155]	Hostile rumination	X		
Difficulties in Emotion Regulation Scale (DERS)	Assess Emotion Regulation	X		
Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency Impulsive Behavior Scale (UPPS-P)	Measure impulsivity	X		

HRV4Biofeedback Survey	Measure emotional state before and after breathing exercise during last 7 days			X
Breathing Prompt	Prompt breathing exercise during last 7 days			X
Website Analysis and Measurement Inventory[156]	Feasibility and Acceptability		X	
Post-Study System Usability Questionnaire[157]	Usability		X	
Client Satisfaction Questionnaire[158]	Client satisfaction		X	

EMA Procedures. Participants will download an application (provided by Ilumivu, Inc.) on their mobile device. We will loan a compatible device and charger to participants who do not own one. Participants will complete a demo session (in person or via Doxy.me) with research staff to learn how to use the mobile device and EMA app and troubleshoot any challenges that arise. Four daily EMA reports will be requested via phone notification (Days 1-28; one morning report plus three subsequent reports at random times over the following 12 hours; i.e., one assessment per 4 hour time block). Participants will have the ability to select the time they receive the morning assessment and provide a daily window for start and end times. Both partners within each dyad will be assigned to the same assessment schedule. Participants will have 2 hours to complete the morning report and 30 minutes to complete subsequent reports, allowing flexibility to make up missed reports. Participants will also be instructed to complete event-driven reports if alcohol use or partner conflict occurs. Reports will include drinking and drug use, self and partner conflict behaviors, and subjective mood and affect. Research staff will contact participants by phone or text if the first two EMA entries on any particular day are missed.

Physiological Assessment and Geolocation. Participants will be issued a Garmin Vivosmart 4 activity tracker and charger and instructed to wear it continuously for 28 days of participation. We will instruct participants to charge the device during sleep to minimize disruption in data collection (60-90 minutes). No participant action is needed to store data from the tracker. EMA data is fully integrated with physiological data and geolocation using Illumivu's cloud-based server. This procedure will allow us to establish temporal sequence and both acute and lagged associations between HRV, drinking, and IPV, and to contextualize findings with geolocation. HRV measurements will be mean-centered for each participant in order to account for participants' baseline ("state"). *Illumivu, Inc. will provide cleaned data and peak, low, and average HRV for each 4-hour EMA assessment period.*

HRV-B Implementation. Participants will be trained at baseline and then will be randomly prompted once daily on days 22-28 to complete 10 minutes of HRV-B according to published protocol[145]. Participants will also be able to use HRV-B more often if they choose. HRV-B will guide participants in an evidence-based paced breathing technique (about 6 breaths per minute)[145,159,160] using visualization on their mobile device of their real-time cardiac parameters[85,161]. This process can reduce sympathetic dominance, enhance autonomic stability, and affect regulation[105,161], which cannot be accomplished by alternatives such as relaxation or deep breathing because participants must learn to breathe at their individualized cardiovascular resonant frequency[162].

HRV-B Usability, Feasibility, and Acceptability. We will assess the number of started, incomplete, and completed HRV-B sessions. Participants will be prompted twice at random intervals to respond to a brief survey assessing HRV-B: 1) ease of use, 2) willingness to continue use, 3) perceived helpfulness, 4) patient satisfaction, and 5) suggestions for modifications. In addition to providing subjective usability, feasibility, and acceptability at the exit interview, participants will complete the Website Analysis and Measurement Inventory (WAMMI)[156], Post-Study System Usability Questionnaire (PSSUQ)[157], and 8-item Client Satisfaction Questionnaire (CSQ)[158]. The investigators will discuss these outcomes and integrate participant suggestions for our planned R01 application.

Compensation. Participants will receive $50 for the baseline assessment, $1 per completed EMA report ($112 maximum), a $10 bonus for each week in which ≥80% of EMA reports are completed ($40 maximum), $10 for the purchase of the HRV4Biofeedback app, $25 for completing all 4 weeks of participation, and $25 for returning borrowed equipment (*return mailers provided*) for a possible $252 total. Participants will be compensated via Clincard, or with check or cash.

STATISTICAL ANALYSES.

General. All data will be collected in a REDCap database to ensure accuracy and validity and analyzed using SAS v9.4 (Cary, NC). Descriptive and summary statistics will characterize the sample and outcomes.

Power and Sample Size. *Based on our enriched recruitment plan of couples with current AUD and IPV, and EMA studies of both healthy community couples and participants with IPV[1,72,163-165], we expect ≥50% of the couples enrolled in this study to report psychological or physical IPV during the 28-day study timeframe.* Within-couple correlation of variables (HRV, alcohol use, IPV) will result in an *effective sample size between N=50 (the number of couples) and N=100 (the number of individual participants)*. For example, for a within-couple intraclass correlation coefficient (ICC) of 0.1 or 0.3, sample sizes approximate *N=90 and N=76*, respectively. At a minimum, the planned sample size *conservatively* provides 80% power to detect within-subject differences in HRV equivalent to Cohen's *d* effect sizes of 0.*3* (the detectable difference with 1 paired set of observations on *the ≥50% of subjects expected to report alcohol use and IPV*), *consistent with those observed in our preliminary studies (see Figure 1)*. However, given the volume of EMA data collected *and despite the fact that many EMA reports will not involve alcohol or IPV, we may even be able to detect much smaller differences*. *For comparisons between partners within a dyad, we anticipate that effect sizes as small as 0.4 and correlations as small as 0.4 will be detectable with 80% power.* Having *N=100* participants will also provide *85*% power to detect whether feasibility and acceptability metrics are lower than 80%. These power analyses assume 2-sided testing and an alpha level of 0.05.

Strengths and Limitations of Design. The long-term goal of this research is to enable the use of wearable technology to identify times of increased risk for alcohol-facilitated IPV due to physiological and emotional over-arousal, and to prepare for an R01 application proposing a randomized controlled trial of HRV-B delivered in a "just-in-time" fashion. These rich multimodal data will establish mechanistic testing procedures and explore patient-specific algorithms predicting optimal HRV-B engagement. Findings will make an essential scientific contribution and will optimize statistical power, HRV-B dose and timing, and participant preferences for our planned R01. This project will be the first to employ unobtrusive wearable technology and geolocation in a study of alcohol-facilitated IPV. A design allowing remote participation is a crucial scientific advancement. Although we will prioritize the analyses above to inform our R01 application, several alternatives were considered. We are equipped to examine additional physiological outcomes, time course of HRV recovery, lagged temporal ordering, and numerous individual, dyadic, and contextual differences in these outcomes. *It is possible that responding to EMA and feasibility/acceptability queries might influence HRV, drinking, or IPV outcomes during the assessment-only or HRV-B period. We have included exploratory analyses to specifically address this possibility and inform future clinical trial design*. The proposed HRV-B dose and timing was selected to provide preliminary data about when, where, and why participants elect to use HRV-B. The primary goal of this project is mechanistic, and intensive prompting or incentivizing HRV-B might confound outcomes. We are equipped to adjust implementation according to data-driven findings in our planned collaborative R01 application.

Summary: This project will use state of the art wearable technology and a novel combination of ecological momentary assessment, continuous physiological monitoring, and geolocation in a micro-longitudinal design. This unique approach, which has never been applied to alcohol-facilitated IPV, will advance the science in this area, elucidate the mechanistic role of HRV in alcohol-facilitated IPV in naturalistic settings, and position the study team to translate findings into a rigorous clinical trial design to mitigate alcohol-facilitated IPV.

HUMAN SUBJECTS RESEARCH

1. Risks to Subjects

Drs. Flanagan (PI), Tomko, and Jarnecke (Co-Is) are licensed clinical psychologists with ample training and experience conducting clinical trials research among individuals and couples with AUD and IPV. Drs. Flanagan, Tomko, and Jarnecke as well as the research assistant have all completed the University of Miami computer-based CITI Human Subjects Research Education Course. All research activity, informed consents, and continuing reviews will be reviewed by MUSC's IRB in compliance with 45CFR46 before the research is started. Continuing review will occur annually. Study staff will ensure that all information needed for the continuing review is consistent with IRB requirements.

A. Human Subjects Involvement, Characteristics, and Design

A total of 50 couples (100 individual participants) between the ages of *21* and 70 will be recruited over a 2-year period. Women and members of minority groups will be eligible for participation and we will strive to enroll an equal number of women and men with AUD. Children ages 18-21 are *not* eligible for participation. Study inclusion/exclusion criteria are as follows:

Inclusion criteria
1) Any gender identity; any race or ethnicity; any sexual orientation; aged *21*-70 years.
2) Married, cohabiting, or in a committed relationship for ≥ 6 months.
3) English fluency and cognitive functioning sufficient to provide informed consent and participate accurately (score ≥ 26 on the Mini-Mental Status Exam [MMSE]).
4) At least one partner within each dyad must meet DSM-V diagnostic criteria for current AUD (assessed by the QuickSCID) *and* current alcohol use based on TLFB.
5) At least one partner within each dyad must endorse ≥1 instance of IPV with their current partner in the past two years (assessed by the Revised Conflict Tactics Scale [CTS-2]).
6) Maintenance of psychotropic medications 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, bipolar, or antisocial personality disorders.
2) Meeting DSM-5 diagnostic criteria for moderate or severe drug use disorder (e.g., cannabis). Concurrent mild drug use disorders are acceptable due to the marked co-occurrence in AUD populations. Moderate or severe Nonalcoholic Substance Use Disorder is acceptable if there has been no current substance use in the last 1-2 months.
3) Alcohol withdrawal as indicated by CIWA-Ar scores >8.
4) Current suicidal or homicidal ideation and intent.
5) Serious cardiovascular health conditions (e.g., *pacemaker, cardiac arrhythmia, hypertension) because the safety of HRV-B has not yet been established in these populations.*
6) Treatment on medications such as lithium, methadone, alpha or beta blockers or cholinergic/ anticholinergic medications likely to confound normative cardiovascular responding.
7) Current neurologic conditions or history of traumatic brain injury.
8) Severe *and* unilateral IPV in the past 6 months.
9) Current pregnancy.

B. Sources of Material

Materials obtained from human participants will include self-report surveys and structured clinical interviews (assessed in the laboratory and remotely using smartphone application), physiological measurements including heart rate and geolocation using a wearable activity tracker, and urine for drug testing.

C. Potential Risks

Confidentiality: Breach of confidentiality is associated with all research that is not anonymous. Realization of this risk could cause negative social or legal consequences. Given that data will be linked to participants' identity between completion of the telephone screening interview and completion of the final assessment, this is an important risk to consider. We believe that the risk is very low, given that most data are collected electronically and all data will be stored securely and separately from identifying data. Several safeguards and procedures for protecting data will be in place (see Adequacy of Protection Against Risks below). 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.

Risks associated with EMA: Risks associated with the EMA portion of the study are minimal and include potential loss of confidentiality (described previously) and the potential for surveys to prompt participants at a time when it is inconvenient or unsafe from them to complete a survey (i.e., while driving). Participants will not only provide

their preferred time window for morning reports, but will also be provided with a time window for completing reports to minimize this risk. They are also informed that some missed sessions are expected and that they are not penalized for a few missed sessions. Participants are asked to sign an agreement stating that they will not complete a session while driving or in any other situation where it is potentially unsafe to do so. The EMA assessments do not provide a method of communicating with research staff in real time. Participants will be informed that study staff will not receive EMA responses in real time and thus it is not a method to communicate directly with the study team or receive assistance. All participants will be provided with a variety of community referrals prior to the start of the EMA component of the project.

Risk for increased IPV *due to research participation*: *This sample will be recruited specifically based on having AUD and a history of IPV in their current relationship. Thus, participants in this project might have instances of psychological and/or physical IPV during the 28-day study period. However, we estimate the risk of IPV occurring, or IPV increasing in frequency or severity to research participation to be very low.* First, Dr. Flanagan has never had a single incident of aggression occur during an assessment or experimental task (e.g., towards partners, research staff, or others) in a study of alcohol-facilitated IPV, *including a recently completed sample of N=100 couples similar to the proposed one, wherein participants were required to meet diagnostic criteria for AUD and have recent physical IPV in their relationship. Dr. Flanagan's team has also not had increased IPV reported in the context of laboratory trials or ongoing couple therapy trials among couples with AUD*. Thus, extensive prior research suggests that the proposed study procedures are safe and the exclusion criteria are effective at minimizing risks of adverse events. Second, in our *recently completed* NIAAA-funded laboratory-based studies of couples with AUD and IPV, post-study debriefing have not detected study-induced aggression or relationship conflict. *In a sample of N=100 couple with co-occurring physical IPV and AUD, no instances of increased subjective aggression or actual IPV were reported.* Dr. Flanagan previously surveyed IPV investigators nationwide (N=59) to identify the frequency, severity, and type of adverse events (AEs) reported in IPV research[166]. Results indicated a low frequency of AEs, strong agreement among investigators regarding safety precautions, and high efficacy of those methods. *These methods, such as private informed consent and assessment apart from one's partner and IPV assessment using validated instruments (CTS-2) will be applied in the current project and AEs will be closely monitored by our team and our DSMB.* While the present study does not include an aggression induction or laboratory aggression task, existing literature in the field of alcohol-facilitated IPV suggest that among men (N=400) surveyed immediately after completing a laboratory IPV task[167], an extremely small proportion (1.8%) reported an increased likelihood of behaving aggressively as a result of participation. Participants denied any specific plans of action and reported one-week later that these feelings did not persist. Rather, they reported that the study made them realize that they could be aggressive and, compared to their prior self-perception of extreme "non-aggressiveness", indicated an increased likelihood of behaving aggressively when provoked in the future. As independent evidence of these results, another research team systematically assessed the post-experiment impact of completing questionnaires, engaging in anger arousing conflict conversations in the laboratory, and being interviewed individually about anger escalation / de-escalation during the conversations among a sample of 85 couples (170 participants) in an intimate partner violence study[168]. In post-experimental interviews, the study was viewed as helpful or neutral by 95.2% of male participants and 96.4% of female participants, both personally and to their relationships. No respondents reported violence as a result of participation. The small number of negative reactions concerned criticisms with particular scales and presumed research hypotheses. Taken together, this evidence indicates that participants' risk of increased aggression as a direct result of study participation is extremely low.

The risk of increased IPV due to study participation is very low primarily because the study team screens out for any severe and/or unilateral IPV at the screening visit. These individuals should not participate in a clinical trial and are referred clinically. This process (referring to higher level of care/clinical provider) is the same for in state and out of state. If the study team becomes aware of increased IPV during the trial, staff will notify the PI, who will consult with the participant(s) privately, thoroughly assess safety and risk and refer clinically. If there is any indication that the study procedures are causing increased IPV, the study procedures will be discontinued immediately and participants will be withdrawn form the study.

2. Adequacy of Protection against Risks

Recruitment and Informed Consent Procedures. All personnel will be trained in the responsible conduct of research. Participants will be recruited from MUSC treatment clinics, community settings, and ads placed on the internet. The screening measure contains questions directly pertaining to the study's inclusion and exclusion criteria. Participants who meet eligibility criteria will be scheduled with research staff for a baseline assessment session. Informed consent will take place in person or via telehealth, using an IRB approved platform, such as Doxy.Me or RedCap. In a private setting apart from their partner, 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. In the event of eConsent, the informed consent process will still take place privately. If partners do not have the ability to each have a private room for eConsent within their residence(s), separate appointments may be arranged to maintain privacy and to meet with each individual partner separately. Informed consent will be collected by, PI (Dr. Flanagan), or trained IRB approved personnel. All study personnel are trained in human subjects research.

Participants will also be informed that they are not required to make a decision about whether or not they choose to participate on that day. Although participants will complete the informed consent procedure apart from their partner to ensure each partner's safety and confidentiality and to minimize coercion, all participants will have the opportunity to discuss participation with their partner prior to providing informed consent. Participants who are eligible to participate and choose to do so will be encouraged to ask any questions they might have about the study. Both the participant and research staff member will sign the form.

The informed consent document will outline 1) the sponsorship of the study; 2) the nature, purpose and procedures of the research study; 3) the voluntary nature of participation (i.e., participation is not required and can be discontinued at any time; 4) duration of the study; 5) potential risks and discomforts and potential benefits of participating; 6) that all information will be kept confidential subject to the provisions of state and federal law; 7) compensation; and 8) alternative treatments. Participants will be informed that they can discontinue participation in the study at any time and that this decision will not influence the care they receive at any MUSC clinic (if they are existing patients of MUSC), regardless if they are located in Charleston, elsewhere in SC or outside of the state of SC.

Assessment Procedures. Some participants may experience distress in response to self-report and interview measures pertaining to alcohol use, IPV, or associated areas of functioning. Our team is equipped with standard operating procedures to conduct baseline inclusion and exclusion interviews remotely using IRB-approved telehealth web platforms such as Doxy.Me, Microsoft Teams or ZOOM. While eConsent and telehealth-based assessment has been enormously successful in Dr. Flanagan's ongoing trials among couples with AUD due to its convenience and accessibility, some participants might determine after attempting that they prefer an in-person appointment. Participants will be informed that they are welcome to change modalities between consent, screening, and exit interview procedures. Participants may also experience physical or psychological discomfort during the study assessments at home. However, based on the research team's past experience and available literature the risks involved in the proposed project are minimal and manageable. Nevertheless, we have a specific protocol in place to manage participant distress in the event that it arises. This protocol is discussed in more detail below. We will also inform participants during the informed consent process that they may terminate study procedures at any point. Our past and ongoing research suggests that the measures and methods proposed in this study can be implemented without undue psychological distress or exacerbation of symptoms. This experience includes numerous federally-funded projects with individuals who use alcohol and drugs.

In the event that a participant becomes distressed secondary to participation, they will be encouraged to contact Dr. Flanagan. In addition, local participants will have access to urgent care services at MUSC treatment clinics. The study team will ensure a local urgent care clinic has been identified for participants who live outside of the Charleston area and outside of the state of South Carolina. Any adverse effects noted by any project personnel will be immediately reported to the PIs, who will then report these adverse effects in writing to the IRB and NIH per protocol (see the Data and Safety Monitoring Plan at the end of this section for more details). The

research team includes several licensed clinical psychologists and a psychiatrist who are equipped to help participants manage distress and to evaluate conditions in which participants need additional assistance. In the event that a participant becomes significantly distressed, the PI will contact the participant later that day to check-in and the following day to ensure they have received necessary resources, and to assess their safety and welfare. If called by participants, the PI will attempt to address all participant concerns and set up a referral for treatment for those who desire it.
Alcohol Withdrawal. Participants will be screened for acute alcohol withdrawal at the outset of the study. Participants reporting CIWA-Ar scores >8 will be excluded from participation and referred clinically.

Confidentiality. Several procedures that have been used previously by the research team will be followed to ensure confidentiality of all participants. Following our established procedures, all research staff are trained in the importance of maintaining confidentiality and will complete the required NIH and MUSC training in protection of human subjects. They will be informed that breach of confidentiality may result in termination of employment and will sign a pledge attesting to their commitment to maintaining subject confidentiality. All presentations of the project data will report findings in terms of groups; no individual identifying information will be presented.

During data collection, data for each participant will be linked to a unique identifier that will be assigned to each participant at the outset of the study. This identifier will be linked to identifying information via a code key until the conclusion of data collection for that participant. The code key linking identifying information to data will be kept on a password-protected computer or locked filing cabinet separate from the data within our team's locked research office. Only key study personnel will have access to this information. Participants who use rideshare services will be required to use their own phones to preserve confidentiality; they will be compensated per the receipt indicated in the scheduling of their transportation.

All computers that will store data for this project are in locked rooms when users are not present. All computers and servers are password-protected. Only individuals with a correct password can gain access to individual computers and servers. To protect individual computers from unauthorized intrusion, computer users do not have administrative privileges on workstations and servers, and therefore are unable to install unauthorized applications and services or modify critical system files that could create vulnerabilities. In addition, firewalls protect each individual computer and server from intrusion. Further, MUSC has additional firewalls and other security devices to protect the network infrastructure from outside their respective campuses. Auditing and password security policies are enabled on computers and servers to track login attempts and restrict unauthorized access.

Most data are collected electronically and all data will be stored securely and separately from identifying data. Paper consent forms will be stored in locked file cabinets in the laboratory, separate from the data. A code key which links participant names to the unique ID number and any hard copies of participants' data will be kept in separate locked filing cabinets. When each participant completes the study, the code key that links his or her identity to their data will be destroyed.

All phones and activity trackers loaned to participants for the purpose of EMA, psychophysiology, and geolocation data collection will be wiped and reset prior to re-issuing the technology to another participant. Study phones will be password-protected and participants using their own devices will be encouraged to enable password protection. Additionally, the smartphone application itself from illumivu requires user identification to complete EMA sessions.

RedCap Data Management and Security. We plan to use REDCap for data capture and management. REDCap (Research Electronic Data Capture) 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. A library of data dictionaries is made available for standards-based data collection forms and validated instruments. 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.

Security of Remote Data Storage Cloud including Physiology and Geolocation. This project will use a cloud-based smartphone application provided by Ilumivu, Inc. in a fee-for-service manner to collect remote ecological momentary assessment data. We will use the same platform through Illumivu for physiological and geolocation data collected via wearable activity trackers. Participants will be informed of the specific data points that will be collected from their particular smartphone (or study smartphone) model and the activity tracker model. Study data will not be shared outside the study team or analyzed for reasons outside the scope of this research project. In addition, the Ilumivu application system allows specific security measures including requiring a user identification and password. The core system implements a hierarchical, roles-based security model that determines access to information and system capabilities. Data files are stored in a secure database and never on the server's file system. Data can be stored in either an encrypted manner or in clear-text. Secure Sockets Layer (SSL) protocols are also implemented using the client's certificate or one acquired by Ilumivu on behalf of its user. All data are encrypted in transmission.

Safety and Monitoring Plan. A procedure for clinical deterioration has been established based upon our experience with previous and ongoing NIH-funded clinical trials. All investigators and study staff will be instructed to use their best clinical judgment regarding emergencies and inform the PI as soon as possible. In addition to relying on clinical judgment on the part of the licensed providers on this team who are experienced with this population, we will also monitor alcohol and drug use, depression, and IPV using standardized measures (TLFB, BDI-II, CTS-2, breathalyzer tests and urine drug screens) in order to detect any symptom worsening requiring further evaluation. Additionally, participants will be advised to observe any signs of worsening alcohol use, depression symptoms, or aggression, and to discuss these challenges with study staff.

Participants will be withdrawn from the study and referred for more intensive treatment if: (1) there are increases in alcohol or drug use leading to the need for a more intensive level of care (i.e., medical detoxification, inpatient or partial hospitalization); (2) there is active suicidal or homicidal ideation and/or intent; (3) there is an inability to manage the participant psychiatrically within the inclusion/exclusion criteria of the study (i.e., need for the initiation of psychotropic medications; development of psychosis); or (4) there is an inability to complete study appointments due to incarceration or hospitalization.

There is a well-established protocol at MUSC for emergency psychiatric evaluation, crisis intervention and/or psychiatric hospitalization for suicidal, homicidal, psychotic or other acutely distressed participants. Immediately on detection of these needs, the assessor/therapist will page a psychiatrist to review the participant's situation. If appropriate, the psychiatrist will personally evaluate the participant. If the participant is in the office, 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.

Participants will be informed during informed consent procedures of the standard limitations of confidentiality such as imminent risk of harm to self or others, or child or elder abuse. Participants will be informed that they can decide not to answer any questions and, should they become distressed or are uncomfortable with continuing to participate, they may discontinue participation at any time without penalty. The compensation schedule will be stated verbally and in writing in the initial study description and the informed consent procedure. The participant's copy of the consent form will provide contact phone numbers and email for the PIs should a participant have any questions, comments, or concerns about their participation. Participants will have the opportunity to have a copy of the consent form mailed to them at any time.

All telehealth participants (in state and out of state) complete a participant locator form with study staff, that allows the study team to identify local emergency care facilities and contact information. Specifically for out of state or remote participants, the study staff will compile a list of referrals and emergency contacts to provide to study participants ahead of enrollment.

Suicide Specific Risk Identification and Response Plan. Specific precautions will be taken to prevent harm to participants and potential participants. Project staff will be supervised by Dr. Flanagan (PI), and Drs. Tomko and Jarnecke (local Co-Is), who are licensed psychologists. All project staff will be specifically trained to assess suicide risk, including ideation, plan, and intent as well as history of ideation or attempts, and they will be trained to develop a safety contract with participants. In initial screening procedures, participants identified by clinical interview with both suicidal ideation and acute intent will be excluded from the study, but will be offered emergency psychiatric care. This care is available 24 hours per day at MUSC, as indicated above. In addition to the assessment measures specified in the Research Plan, the Beck Depression Inventory-II will be administered. Any participant any participant scoring above 25 on the BDI-II (administered at each visit) or answering a "1" or above to question 9 will be specifically queried about suicidal ideation and intent. In any instance where ideation or intent is identified, the PI will be immediately notified and will contact the participant for further evaluation. If both ideation and intent are present, the aforementioned hospital intervention will be provided. Thus, all assessment points represent suicide risk identification, assessment, and intervention opportunities. Study staff will be specifically trained regarding the increased risk of suicide in Veterans, and will receive specific instruction of suicide risk assessment, should a Veteran be enrolled.

All telehealth participants complete a participant locator form with study staff, that allows the study team to identify local emergency care facilities and contact information. Specifically, for out of state or remote participants, the study staff will compile a list of referrals and emergency contacts to provide to study participants ahead of enrollment. Ahead of appointments that are taking place outside of the Charleston area (both in SC and outside of SC), the study team will ensure a local (to participant) emergency line has been identified. In the event of a true emergency, the study team can contact the local authorities or emergency dispatch to send help to participant.

Study Implementation and Data Security. We will take careful precautions to maintain confidentiality for all participants, using procedures we have used with similar previous studies: All research personnel will attend a required in-service training conducted by the PI where the screening, informed consent, and assessment protocols will be described. All members of the research team will sign a confidentiality agreement that no identifying information of specific individuals will appear in any external documents (e.g., peer-reviewed publications, presentations) or in any internal reports.

All study data related to study outcomes (i.e., urine drug screens, participant responses to questionnaires and interviews, EMA data, geolocation) and demographics will not have any unique identifying data attached in any way. All participants will be assigned a numerical study identifier to minimize the potential to link identifying information with study data. One master list of study participants will be kept separate from all other study data. The master list will be destroyed upon study completion; it will be kept separate from all data and will be available only to the PI, Study Coordinator, and research assistants. To protect participant confidentiality, all data will be maintained in a manner consistent with IRB-approved protocol. Data will be entered directly into RedCap wherever possible. If paper data is necessary, it will be stored in locked filing cabinets within a locked office and on MUSC's encrypted computers and data servers. Access to de-identified study data will be limited to named project investigators, the Study Coordinator, NIH audit personnel and MUSC IRB audit personnel. Data will be maintained per IRB-approved protocol.

The study protocol and safety plan will be printed and kept in a central location within the research space for easy access, and on the MUSC server. Standard operating procedures (SOPs) for the management of any participant or study-related emergency will be established and research staff will be trained on these protocols. All participant assessments will be scheduled during normal working hours on the MUSC campus or remotely to ensure clinical staff are reachable and the safety of participants and research staff is maintained. After-hours appointments will be scheduled in advance and study staff will ensure clinical staff and/or PI are on call for any after-hours appointments.

All research staff has completed or will complete the University of Miami CITI training course in the responsible conduct of research. Necessary certifications in the responsible conduct of research and the protection of human research participants will be completed on an annual basis, in compliance with MUSC institutional and NIH regulations.

3. Provisions to Monitor the Data to Ensure the Safety of Subjects

Trial Management. Dr. Flanagan (PI) will be responsible for monitoring the trial. 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. Flanagan (PI) will be responsible for distinguishing between serious (SAEs) and non-serious adverse events (AEs), and determining study relatedness.

DSM Board. 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 includes 2 researchers with experience in treating patients with 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. AEs are reportable to the local Institutional Review Board (IRB) if the AE is unexpected AND related or possibly related AND 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. All AEs will be reviewed by the PI, and annually by the Data and Safety Monitoring Board (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 visits 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 and Study Physician at the weekly study team meeting.

Safety Reporting. All unexpected AEs will be reported to the MUSC IRB and NIH within 10 working days. AEs are reportable if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. 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 by the PI, and annually by the DSMB and IRB. Any significant actions taken by the local IRB and protocol changes will be reported to NIAAA. An annual report summarizing all AEs will be provided to the NIAAA project officer. This report 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.

4. Potential Benefits of the Proposed Research to the Participants and Others

While there is no guarantee of specific benefit to participants in this study, the potential benefits include a thorough psychological and substance use assessment, referral to appropriate treatment services and community resources, and remuneration. Other study benefits include contact with research staff, access to assessment

information pertaining to mental health, substance abuse, and relationship functioning, and referral to treatments for associated problems such as mental health concerns and smoking. 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 the state of the science in prevention and treatment for individuals who drink alcohol and experience IPV. Given our safety protocols and our team's safety history, we feel that the scientific and societal benefits of the project far outweigh the minimal risks involved.

5. Importance of Knowledge to be Gained

There is considerable knowledge to be gained from the proposed study. Alcohol is a well-established precipitant to IPV and alcohol-facilitated IPV is a significant and persistent public health concern. Detailed etiological models explaining the behavioral and pharmacologic associations between acute alcohol intoxication, AUD, and IPV have also been developed from this important prior work. However, despite emerging data regarding physiological underpinnings of alcohol-facilitated IPV and data supporting heart rate variability biofeedback (HRV-B) interventions in other areas, no studies have examined respiratory sinus arrhythmia measure of HRV as a mechanism of alcohol-facilitated IPV in naturalistic settings. Thus, this study is essential to (1) develop a clear and testable model of the mechanistic role of HRV in alcohol-facilitated IPV etiology, and (2) provide preliminary data on HRV-B as a possible pathway through which alcohol facilitated IPV can be prevented or reduced. To address this urgent need, the present study is the first to employ accessible state of the art wearable technology and to leverage a unique combination of self-report, EMA, physiological, and geolocation data. The findings from this study will provide essential preliminary data to significantly advance the state of the science in this area, refine and optimize a dynamic and accessible treatment target (HRV-B) to reduce alcohol-facilitated IPV, and translate findings into a rigorously designed collaborative R01 proposal.

6. Device

This project involves the use the Garmin Vivosmart 4 activity tracker, an exempt medical device per IDE regulations 21 CFR 812.2(c), as it is a legally marketed device used in accordance with its labeling. Garmin wearables are not medical devices, and the data provided by them is not intended to be utilized for medical purposes and is not intended to diagnose, treat, cure, or prevent any disease. The standard software development toolkit is HIPAA-compliant, allowing the study team to aggregate and archive the data on secure MUSC servers and systems. .

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