CALIBRATION STUDY OF A WEARABLE NONINVASIVE BLOOD ALCOHOL MONITOR

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1 List of Abbreviations

Abbreviation	**Abbreviation definition**
Area under the concentration–time curve	AUC
Alcohol Use Disorder	AUD
Blood Alcohol Concentration	BAC
Blood Alcohol Level	BAL
Breath Alcohol Concentration	BrAc
Clinical Institute Withdrawal Assessment	CIWA
Concentration Maximum levels	Cmax
Columbia Suicide Severity Rating Scale	C-SSRS
Electrocardiogram	ECG
General Clinical Research Unit	GCRU
Repeated Measures Correlation Coefficient	RMCC
Time-Line Follow-Back	TLFB
Transdermal Alcohol Concentration	TAC
Time to reach the Cmax	Tmax

2 Protocol Summary

Title:	Calibration Study of a Wearable Noninvasive Blood Alcohol Monitor
Population:	The present study will involve 12 men and women aged 21 to 55 who drink regularly and occasionally binge-drink. Women and minorities who meet the study criteria will be eligible to participate. No vulnerable populations are being targeted for inclusion in this study
Intervention:	Eligible subjects will receive alcohol in the laboratory setting. Subjects will complete a drinking session designed to raise BAL to 0.05 g/dL. Data from this drinking session will be used to calibrate wristwatch sensors with BAL measured by a breathalyzer. Subjects will return for a second drinking session following completion of the calibration trial. Data from this second trial will be used to validate the calibration model. During both drinking sessions subjects will have access to streaming entertainment. BAL will be measured continuously with wristwatch sensors, and every 15 minutes with a breathalyzer.
Objectives:	This NIH SBIR Phase II study addresses development of a new, noninvasive wrist-mounted device for measuring blood alcohol. This wristwatch platform with modern smartwatch capabilities will move the state of innovation forward in the noninvasive alcohol monitoring field and will contribute societal benefits in the form of facilitating alcohol research and treatment. Additional benefits include providing blood alcohol monitoring to consumers interested in health and fitness, employer wellness programs and other medical and judicial system uses. If successful, the transdermal alcohol sensor could be used in clinical research as an objective measure of drinking outcomes.
Design/Methodology:	This trial is designed to generate data that will be used to build a model that will transform transdermal alcohol readings into an approximate measure of breath alcohol level. The ultimate goal is to test the accuracy of a wristwatch BAL monitor relative to alcohol breath testing once this model has been completed. An established human laboratory self-administration procedure will be followed. Each subject will complete 4 clinic visits over a period of up to 9 months of participation. Study participation is comprised of 1) a baseline assessment to determine eligibility 2) an alcohol self-administration trial to develop a model for correlating transdermal alcohol with breath alcohol readings, 3) a follow-up assessment to confirm eligibility to continue, and 4) an

	alcohol self-administration trial to test the accuracy of the wristwatch BAL monitor .
Total Study Duration:	The entire study will take 12 months to complete.
Subject Participation Duration:	Each subject's length of participation will be up to 9 months.

3 Background/Rationale & Purpose

3.1 Background Information

The goal of this study will be to continue development and commercialization of a new noninvasive transdermal alcohol monitor developed by KWJ Engineering, Inc. The wrist-mounted transdermal ethanol measurement system being studied in this proposal is part of the modern trend toward wearable and noninvasive measurements. In recent years there has been a growing trend in science and technology toward developing noninvasive on-body, continuous measurements in the management of chronic disease, monitoring the elderly, diagnostic sensing and other biomedical applications [1-7]. Stretchable and flexible materials for dermal sensors are emerging, as are new approaches to making physical and chemical measurements noninvasively on the skin [8-11]. KWJ engineering is an industry-leading manufacturer of monitoring sensors, instruments, and gas sensors designed to reduce risks to health, safety, and security in commercial and consumer environments. KWJ has recently received an SBIR phase II award from NIAAA to continue efforts to develop a wearable transdermal sensor that monitors Blood Alcohol Level (BAL) in real-time. The monitor is based on the KWJ Engineering's printed electrochemical gas sensor that is able to detect ethanol concentrations in the skin. This ethanol sensor is a very small, ultralow power, and highly sensitive device with very low interferences. In previous studies leading up to the SBIR award, KWJ Engineering has demonstrated stable and sensitive measurement of ethanol across human skin surrogate membranes. This was accomplished with an initial prototype wristwatch device that included the ethanol sensor and circuitry for performing the measurement and converting data for wireless communication to a computer. Raw transdermal ethanol concentrations were calibrated to blood alcohol values using standardized ethanol solutions as a surrogate for blood alcohol concentration (BAC). KWJ has demonstrated a high degree of reproducibility in measurement sensitivity across several watch format devices.

3.2 Rationale and Purpose

In this proposed study, the objective is to further demonstrate the reliability of this printed electrochemical gas sensor in the form of a wearable device. This demonstration of reliability among human subjects is an essential part of product development. The monitor will be in a wristband or watch form, similar to a smartwatch. It will also have smartwatch features including measuring key physiological parameters (e.g., pulse) and eventually will have connectivity to apps on smartphones and other devices. The aim of the work is to provide a new, noninvasive transdermal alcohol monitor into the market. The transdermal alcohol monitoring market has few wearable products available and innovation has been lacking in this field. Developing a new wearable alcohol sensor could have many applications. For example, people interested in health and fitness who want to better track their alcohol intake. This may be particularly beneficial to

individuals who seek to reduce the risk of alcohol use by limiting peak BAL. This technology could be adapted for use in clinical trials where measurement of alcohol consumption is typically the primary outcome measure. Although the current "gold standard" for measuring alcohol use (the TLFB method) has acceptable reliability and validity, a wristwatch might offer advantages over the TLFB given the potential for precision of data that cannot be achieved with the estimation methods used with the TLFB. A wristwatch sensor may also offer an objective means of data collection that is less vulnerable to the risk of subject deception or intentional minimization. Additionally, there is a certain degree of subject reactivity to completing drinking assessments on a weekly basis that alters the course of drinking. If successful, this wristwatch may provide a means for assessing alcohol consumption without subjects reacting to the assessment methodology. This technology could also be adopted in many areas including clinical and medical treatment, employee wellness programs, alcohol, and as part of brief interventions that target at-risk drinkers.

4 Objectives

4.1 Study Objectives

The specific objective of this study is to determine whether the printed electrochemical gas sensor designed to measure BAL will be sensitive and reliable when compared to a standard measure of BAL taken by a breathalyzer (Intoximeter Alco-Sensor IV). If this sensor proves sensitive to changes in BAL and can reliably measure BAL relative to a "gold standard" method, there are significant opportunities to use this technology in consumer health applications and clinical research.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

The primary outcome is the correlation in estimated BAL as measured by the breathalyzer and the wristwatch sensor during the second alcohol self-administration trial. BAL and wristwatch sensor data correlation will be analyzed by repeated measures correlation (rmcorr) analysis, as described in more detail in section 12.

4.2.2 Secondary Outcome Measures

In addition to the determination of correlation between BAL and transdermal alcohol concentration (TAC) as measured by a reference breathalyzer and the developmental KWJ wrist device, respectively, we anticipate that Phase I of this study (the first alcohol self administration trial) will provide a means to determine the characteristic time lag between BAL and TAC [12] and furthermore allow development of a preliminary model for correcting TAC measurements for this lag.

5 Study Design

This is a device calibration study designed for healthy non-treatment-seeking drinkers. The drinking lab portion of this study is an adaptation of an established human laboratory self-administration procedures [13]. Subjects who consent to this study will complete two alcohol self-administration sessions, one in the Calibration phase (Phase I) of the study and one in the Validation phase (Phase II) of the study.

Calibration Phase I. The calibration phase of this study is designed to gather data to assist in developing an equation to account for the lag in TAC readings and transform these readings into an approximation of alcohol breath readings. In this calibration phase subjects will be given a measured dose of alcohol to achieve a peak BAL level of 0.05 g/dL after a one hour drinking session. The volume of alcohol will be calculated using an online tool developed by UW-Madison (http://dionysus.psych.wisc.edu/WebCMS/baccalc.htm) based on a formula described by Watson [14]. The hour-long drinking session will be followed by a five hour observation period to ensure that subject reach peak TAC. Blood alcohol level will be measured simultaneously using the transdermal sensors and the breathalyzer for the duration of the drinking period and observation period. Breathalyzer readings will be taken every 15 minutes during the entire experiment and transdermal sensors will log data continuously. To ensure residual alcohol in subjects' mouths does not provide a false breath alcohol reading, subjects will rinse their mouth twice with water after consuming a saltine cracker prior to each breathalyzer given while the subject is consuming alcohol. Subjects will remain in the drinking lab for up to five hours to allow for measurement of the peak transdermal alcohol concentration. Given the length of observation, we estimate that subjects will fully metabolize the alcohol they received during the calibration session and they will have a BAL of 0.00 g/dL when the calibration session is over. In the event that a drinking session is halted or the subject has a very slow rate of metabolism, we require that subjects remain in the laboratory until their BAL, as measured by breathalyzer, reaches 0.04 g/dL or less. The drinking session will be video-recorded to provide a record of the exact timing of breathalyzer readings. If methodology or safety issues are uncovered during the Phase I of this study, the protocol may be amended to address these issues prior to completing Phase II.

Validation Phase II. Data from Phase I of this study will be used to develop a model to account for the lag in transdermal sensor readings relative to breathalyzer readings. Once all subjects have completed Phase I and the calibration model is complete, subjects will return to the laboratory to complete Phase II of the study. Given the expected time lag between Phase I and Phase II, eligibility will be re-assessed prior to the Phase II drinking session to ensure subject safety (see appendix A for schedule of events). If the subject remains eligible for Phase II of the study, the Phase II validation drinking session will be scheduled within 14 days of re-assessing eligibility. During the validation drinking session subjects will be given a measured dose of alcohol to achieve a peak BAL level of 0.05 g/dL after a one hour drinking session. The drinking period will be followed by a three-hour observation period. Blood alcohol level will be measured simultaneously using the transdermal sensors and the breathalyzer for the duration of the drinking period and observation period. Breathalyzer readings will be taken every 15 minutes during the entire experiment and transdermal sensors will log data continuously. To ensure residual alcohol in subjects' mouths does not provide a false breath alcohol reading, subjects will rinse their mouth twice with water after consuming a saltine cracker prior to each

breathalyzer given during the drinking period. Subjects will remain in the laboratory until their BAL, as measured by breathalyzer, reaches 0.04 g/dL or less.

Subjects: Subjects will be recruited through radio advertisements, newspaper advertisements, study flyers, social media, and internet postings. Interested subjects will be screened by telephone to determine initial eligibility prior to the baseline assessment.

6 Potential Risks and Benefits

6.1 Risks

Physical discomforts:

The drawing of blood may cause pain, bruising, lightheadedness, and on rare occasions, infection. Subjects may briefly feel the prick of the needle when it is inserted. Subjects may feel dizzy or faint when blood is drawn. Trained phlebotomists will be used to minimize these risks.

ECGs may cause discomfort and/or irritation of the skin (redness and itching) from the adhesive electrodes. Hair on the subjects' chest may need to be removed in order to obtain the best electrical contact between the adhesive electrodes and subjects' skin. Trained staff will be used to minimize these risks.

Risk to recovery efforts

Treatment-seeking drinkers will be excluded from this study to minimize the risk that drinking in the laboratory could worsen outcomes for a subject trying to reduce or abstain from alcohol. All subjects will undergo a medical screening and we will exclude subjects who have a medical or mental condition for which alcohol exposure in this study would be contraindicated. All subjects will receive the NIAAA self-help guide *Rethinking Drinking* at the end of study participation [15].

Risk of overconsumption

To minimize the risk of subjects reaching a level of intoxication that is uncomfortable to them, we will remind subjects that they may discontinue study participation at any time. Subjects who qualify for this study will have experience consuming alcohol at an amount similar to the dose chosen for this study. Subjects will be monitored during the course of the study. Medical staff will evaluate subjects and may make a determination to halt study participation if the subject becomes too behaviorally impaired or if there are emergent safety issues. During the descending BAL period, subjects will have access to a comfortable space with entertainment (streaming media), snacks, non-alcoholic beverages, and a nearby bathroom.

Subject release:

- Subjects who have a BAL greater than .04 g/dl or who appear to be too behaviorally impaired to leave our research center will be asked to remain in the clinic until their

intoxication is reduced to a level that it is safe to discharge them from the research laboratory.

- Subjects will not be released within 60 minutes of their last drink consumed to ensure that peak BAC has been reached prior to discharge.
- Onsite medical supervision (study RN or GCRU RN) will be maintained while the subjects are in the lab until the time of discharge (<0.040 g/dL) or until they reach a BAL = 0.000 g/dL

Risk of loss of confidentiality

There is some risk that health information collected as part of this study could be seen by unauthorized individuals. Every effort will be made to minimize this risk and protect subject confidentiality. Electronic data will be housed in the REDCap data management system. REDCap is protected via Secure Sockets Layer (SSL) encryption that provides access restriction options. Exported data from REDCap will be stored on a secure password-protected server behind the BMC firewall. Source and CRF binders will be stored in a double-locked area that is accessible to only study staff. Subjects will be assigned a study identification number and this will be used to code any forms that do not require the subject's direct identifiers (e.g., consent form, laboratory results, and contact information). A linking key that associates study ID with direct identifiers will be stored in a double-locked cabinet accessible only by study team members. Data will be stored on a password-protected computer accessible only to the study team. Video of subjects during the drinking session will be stored on an encrypted drive with password protection. Video files will be deleted at the end of the study. All study staff will receive appropriate training for the protection of human subjects (NIH Protecting Human Research Participants, CITI Training). A certificate of confidentiality will be sought to protect subjects from disclosure under court order or subpoena.

Psychiatric risk

We do not anticipate that study procedures will have risk for psychiatric problems. Although we are excluding people with suicidality, it is possible that subjects will identify suicidal ideation or behavior either in screening or during the study. To minimize the risk of worsening suicidal thoughts and behaviors we will monitor suicidal thoughts and behaviors using the Columbia-Suicide Severity Rating Scale and the MINI Neuropsychiatric Interview. Subjects with a MINI suicidality score greater than 8 (low risk) will be excluded. Subjects who report any active suicidal thoughts or behavior as measured the C-SSRS will be excluded from participation. In addition to excluding active suicidality, the MINI will be used to rule out subjects who have psychiatric conditions that may increase the risk of the occurrence of suicidal thoughts or behavior (e.g., major depression, bipolar disorder). Assessment and scoring of suicide rating scales will be conducted in real-time while the subject is present. Suicidality will be assessed by trained clinical staff including study MDs, a psychologist, a nurse, and a mental health counselor. If subjects are found to be at risk for self-harm, study staff will work with the subject to develop a safety plan that could include escorting the subject to the BMC ED or calling BEST.

6.2 Potential Benefits

Although there is no potential direct benefit to participation, this study presents a strong potential for benefit to science. There are very few objective measures of alcohol consumption that can be used to determine outcomes in clinical trials for people with alcohol use disorder. Among the objective measures that are available, data about drinking is limited with regard to accurate measurement quantity and frequency of consumption. A wearable wristwatch that accurately measures BAC could be used to calculate the timing, frequency, and quantity of drinking as a continuous measure throughout an alcohol treatment study. This device also has significant potential value as a consumer device that could be used as a tool to help people achieve a goal of less risky drinking.

6.3 Analysis of Risks in Relation to Benefits

The most significant risk of this study is consuming alcohol. We have chosen a dose that is consistent with the baseline drinking of our targeted sample, and we have included appropriate protections to safeguard the well-being of our subjects. With the protections we have in place for all the potential risks in this study, we believe the risks of this study are well minimized. The study holds significant promise for helping to develop new technology that could be used in both clinical trials and the consumer market. We believe the risk/benefit ratio is favorable.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. 21-55 years of age.
2. Can provide proof of age with state or federal picture ID.
3. Consumes an average of ≥7 standard drinks per week (women) or ≥14 drinks per week (men) over the 28 days prior to consent.
4. Has consumed at least 4 standard drinks on a single day on at least two days in the past 28 days prior to consent.
5. Has a BAL = 0.000 at time of consent.
6. Is able to understand and provide written informed consent.
7. Body weight ≥ 120 lbs and ≤ 250 lbs
8. Subjects can speak and understand English

7.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Currently seeking treatment for alcohol problems or purposefully abstaining from alcohol in an attempt to cut back or quit drinking.
2. Clinical Institute Withdrawal Assessment at ≥10.
3. Meets DSM-5 diagnosis of current major depression, bipolar disorder, schizophrenia, bulimia/anorexia, dementia, or a substance use disorder other than alcohol, nicotine, marijuana, or caffeine

4. If female, pregnant or nursing.
5. If female, does not agree to use an accepted form of birth control
6. Has medical or mental condition for which further alcohol exposure at the planned dose range would be contraindicated.
7. Taking medication for which drinking would be contraindicated.
8. Clinically significant abnormal ECG.
9. AST or ALT ≥ 3x the upper limit of normal.
10. Current risk of suicidality.
11. Has taken medications that are used to treat AUD in the past 90 days.
12. Has received alcohol counseling or other non-pharmacologic intervention to treat AUD in the past 90 days.
13. Has urine toxicology results positive for cocaine, opioids, amphetamines, buprenorphine, methadone, or methamphetamines.
14. Smokes greater than 5 cigarettes per day.
15. Unable to comfortably abstain from nicotine for a period of 8 hours.
15. Wearing cologne, perfume, aftershave or any other scented oil or alcohol-based beauty product on the day of the Alcohol Lab Visit.
16. Has dietary restrictions that would preclude participating.

8 Study Intervention

This is a non-interventional study.

9 Study Procedures

Study Overview: Each subject will complete 4-5 clinic visits over a period of up to 9 months of participation. Study participation is comprised of a baseline assessment, Phase I BAL calibration session, Phase II eligibility determination session, and Phase II BAL validation session.

Baseline assessment

Consenting subjects will undergo a general medical screen, including medical history physical examination. Drinking will be assessed using the TLFB [16], alcohol withdrawal using the Clinical Institute Withdrawal Assessment [17], and suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS) [18]. Exclusionary mental health conditions will be assessed using the MINI Neuropsychiatric Interview for DSM-5 [19]. Subjects will undergo urine toxicology and a urine pregnancy test for women of child bearing age. The baseline assessment may be completed in one or two visits.

Phase I BAL Calibration session:

Subjects will return to the laboratory within 14 days after completion of the baseline assessment to complete the Phase I BAL calibration session. For safety reasons, subjects will be asked to arrange transportation plans for this study visit. The alcohol lab visit is divided into four phases: 1) Screening, 2) Zero BAL observation, 3) Alcohol Administration, and 4) Observation.

1) *Screening*. Eligibility to continue in the study will be confirmed in a brief screening session. Subjects will undergo vital signs, alcohol breath test, urine drug screening, assessment of concomitant medications, assessment of alcohol withdrawal, urine pregnancy testing (for women), adverse event assessment, suicidality screening, and assessment of drinking since the

baseline. Blood alcohol level must be 0.000 to continue with the study procedures. Subjects will be excluded if urine toxicology results positive for cocaine, opioids, amphetamines, buprenorphine, methadone, or methamphetamines. Subjects will also be excluded if any concomitant medications that present safety issues for drinking have been started since the baseline assessment. Subjects will be excluded if the CIWA ≥10 or if the C-SSRS indicates any current suicidal ideation or behavior.

2) *Zero BAL observation*. Subjects will be escorted from the Clinical Studies Unit to the General Clinical Research Unit (GCRU) for the remainder of the alcohol lab visit. The room in the GCRU that will be used is carpeted and furnished with a lounge chair, side table, table lamp and television which allows access to popular streaming entertainment (e.g., Netflix, YouTube, and HBO-GO). A small unobtrusive camera is mounted in one corner to allow for monitoring without study staff being present in the room. During the Zero BAL observation period (and all subsequent phases in the GCRU) study staff and subjects will be instructed not to use any alcohol-based sanitizing hand cleaners due to the potential for interference with the BAL wristwatch sensor. During the Zero BAL session study staff will fit the BAL wristwatches on subjects and begin a 1-hour period of baseline monitoring of a zero BAL. This observation period will be used to demonstrate that the BAL wristwatches do not provide false positive readings under zero BAL conditions. Study staff will measure BAL every 15 minutes during this 60-minute observation period using a breathalyzer. Subjects will have access to streaming entertainment during this period, but will be asked to limit use personal electronics for the duration of the zero BAL session.

3) *Alcohol Administration*. After 60 minutes of Zero BAL observation the drinking self-administration session will begin. At the start of the alcohol administration session the subject will be given a pre-determined volume of alcohol designed to raise BAL to 0.05 g/dL. The volume of alcohol will be calculated using an online tool developed by UW-Madison (http://dionysus.psych.wisc.edu/WebCMS/baccalc.htm) based on a formula described by Watson[59]. The hour-long drinking session will be followed by a five hour observation period to ensure that subject reach peak TAC. Blood alcohol level will be measured simultaneously using the transdermal sensors and the breathalyzer for the duration of the drinking period and observation period. Breathalyzer readings will be taken every 15 minutes during the entire experiment and transdermal sensors will log data continuously. To ensure residual alcohol in subjects' mouths does not provide a false breath alcohol reading, subjects will rinse their mouth twice with water after consuming a saltine cracker prior to each breathalyzer given while the subject is consuming alcohol. Subjects will have access to streaming entertainment during this period, but will be asked to not use personal electronics for the duration of the self-administration session. This drinking session will be video recorded to confirm exact times of BAL readings taken with the breathalyzer. Subjects will remain in the laboratory until their BAL, as measured by breathalyzer, reaches 0.04 g/dL or less.

4. *Observation.* Subjects will remain in the drinking lab for five hours of observation following alcohol administration. Breathalyzer readings will be taken every 15 minutes during the observation and transdermal sensors will log data continuously. Data from this observation will be used to develop a model that adjusts for the lag in peak TAC relative to measured BAL using a breathalyzer. Subjects will continue to have access to streaming entertainment and will also

have access to any personal electronic devices for this phase. Subjects will consume crackers and water just prior to the first breathalyzer reading during this phase. This observation period will be video recorded to confirm exact times of BAL readings taken with the breathalyzer. Subjects will be monitored during the observation until their blood alcohol level is ≤ 0.0 g/dL and they are not behaviorally impaired to leave. Four hours after consuming alcohol subject will be given a light meal that is approximately 375 calories. Study staff will assess intoxication, sedation, and adverse effects during this observation period. Subjects will also have access to snacks (e.g. chips, granola bars) and non-alcoholic beverages if the time needed to reach ≤ 0.04 g/dL exceeds the 5-hour observation period. Subjects will be required to have a plan for transportation home that does not involve driving or riding non-motorized transportation (e.g., bike, scooter).

Phase II eligibility determination session

Once all subjects have completed phase I of the study and the model for adjusting TAC readings has been developed, subjects will be invited back to the lab to complete phase II of the study. Eligibility will be re-assessed to ensure subject safety prior to completing the second drinking lab (see appendix A for schedule of testing events).

Phase II BAL validation session

Within 14 days of subjects completing the Phase II eligibility Determination session, subjects will return to the clinic to complete the Phase II BAL validation session. This second alcohol lab visit is divided into the same four phases as the Phase I BAL calibration session: 1) Screening, 2) Zero BAL observation, 3) Alcohol Administration, and 4) Observation. The procedures for this second alcohol lab session are the same with a few exceptions:

1) Subjects will be wearing second generation wristwatch sensors.
2) TAC readings will be converted into estimated breathalyzer BAL readings based on the model developed in Phase I.
3) The observation period will last only 3 hours (or longer of needed for BAL to reach ≤ 0.04 g/dL).

If a subject completes Phase I and is unable to complete Phase II for any reason, replacement subjects will be recruited to complete Phase I and II consecutively. It is estimated that 36 subjects will be consented to yield 12 subjects that will complete Phase I and 9 subjects that will complete Phase II. Based on past experience with subject attrition, it is estimated that 33% of the Phase I subjects will be replaced at the time of phase II. Given the sample size requirements for this study are 9 subjects to complete both trials, the total sample size is estimated to be 12 subjects taking into account the possibility that three subjects will be lost to follow-up between trials one and two. If subjects are lost, when these subjects are replaced they will complete both the calibration session and validation session over the period of approximately 60 days.

Subject compensation

Subjects will be compensated up to $340 for completion of all study activities. In addition to reimbursements for each study visit, subjects who complete all study visits will receive a completion bonus at the end of the study. If at any time subjects are discontinued from the study during a visit, subjects will be paid a portion of the payment based on time completed (e.g., 1

hour completed of two-hour visit = 1/2 of payment). Note there is an exclusion for payment due to UDS+ at the baseline.

Subjects will receive the following reimbursements:

Baseline assessment	$40
Phase I BAL Calibration session	$100
Phase II eligibility determination session	$40
Phase II BAL validation session	$100
Completion Bonus	$60

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10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 Definitions

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Participation in the research does not include the time between Phase I and Phase II of the study. Subjects will not be monitored for adverse events in the time between Phase I and Phase II as there are no study activities during this time period.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

10.2 Safety Review

Both the risks listed in Section 6.1 and unknown risks will be monitored as follows:

Adverse events will be monitored from the time of study consent through the end of the first drinking session. Adverse events will not be monitored in the estimated 9 months between drinking session 1 and drinking session 2 as there are no study activities in this period. Adverse event monitoring will resume when the subject returns to complete assessment prior to the second drinking session, and it will continue until the subject has completed the study.

Adverse events will be monitored by medical staff using the "adverse events" CRF. Adverse events will be assessed on the alcohol self-administration day. If a subject has an ongoing SAE or unanticipated problem at the time that the subject completes all study procedures, Adverse Event assessment will continue until satisfactory resolution (either resolved or stabilized and is not expected to resolve in the near term) of the event or problem.

For each recorded AE or SAE, the study MD staff or study nurse will assess expectedness based on the known risks of study participation. The study MD staff or study nurse will also assess severity based on the following criteria:

Mild: An event that is usually transient, requiring no special treatment, and does not generally interfere with the subject's daily activities.

Moderate: An event that interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject. The event is usually ameliorated with additional specific therapeutic intervention.

Severe: An event that interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the

Mild:	An event that is usually transient, requiring no special treatment, and does not generally interfere with the subject's daily activities.
	subject and hospitalization may be required, and typically requires intensive therapeutic intervention.
Life-threatening	An event that puts the subject into imminent risk of death without intervention.

Study staff will assess whether AEs and SAEs are unexpected:
Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

The study MD staff or study nurse will assess AE/SAE relationship to the study procedures based on the following criteria:

Unrelated:	The temporal sequence of the AE/SAE onset relative to study procedures is not reasonable, or there is another obvious cause of the AE/SAE.
Unlikely:	It is possible that the AE/SAE is related to exposure to study procedures but there is another more likely cause of the AE/SAE.
Possible:	The temporal sequence of the AE/SAE onset relative to study procedures is reasonable, but the AE/SAE could have been due to another equally likely cause.
Probable:	The temporal sequence of the AE/SAE onset relative to administration of the study procedures is reasonable, and the AE/SAE is more likely explained by the study procedures than by any other cause.
Definite	The temporal sequence of the AE/SAE onset relative to administration of study procedures is reasonable, the AE/SAE is more likely explained by the study procedures than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the risks of study procedures.

10.3 Stopping Rules

There are no interim analyses planned that would allow for a determination of futility or overwhelming benefit. Study enrollment will be suspended under the following circumstances:

1. Serious Adverse Events. Study enrollment will be suspended in the event of a single serious adverse event that is determined to be unexpected and at least possibly related (i.e. it is an Unanticipated Problem). If suspended, study recruitment will not continue until a determination has been made about whether the known risks of participation have changed and the BU Medical Campus/Boston Medical Center IRB has made a finding that the risk/benefit ratio remains favorable given the possible newly identified risk.

2. Risk of intoxication. Subject recruitment will also be suspended if more than one subject of the first ten subjects enrolled is discontinued by the investigator due to intoxication during the alcohol self administration trial. Due to differences in alcohol tolerance, BAL is not a reliable measure of subjects potentially posing a safety risk. Medical staff will make a subjective determination of risk based on the subject's behavior. After 10 subjects have been enrolled, the trial will be suspended if there are more than 10% of subjects whose participation has been halted by the study team due to concerns about physical safety because of intoxication during the alcohol self-administration trial. If suspended for this reason, the study team will consider design changes to reduce the likelihood of this as a potential risk to study subjects. Recruitment would resume when the BU Medical Campus/Boston Medical Center IRB has made a determination that proposed changes to the study design have an acceptable risk/benefit ratio.

10.4 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

11 Data Handling and Record Keeping

11.1 Confidentiality

All staff will be fully trained in the procedures for protection confidential health information. To maintain subject confidentiality, study data will be coded on CRFs that are identified by a subject

number only. Source records with identifying information and CRFs will be stored in double-locked space with access only by authorized staff. Data stored in the REDcap system will have strong protections including file encryption and password access. Subject information will not be released without written permission. Upon approval of the study by an IRB, an application will be filed with NIAAA for a Certificate of Confidentiality.

11.2 Source Documents

Source documents in this study include:
Laboratory test results
Photocopies of the urine drug screening test result
ECG tracings
Subject locator form
Subject contact form

Data generated by the methods described in the protocol will be recorded in the subjects' source binder. Data may be transcribed legibly on CRFs for each subject or directly inputted into an electronic system or any combination thereof.

11.3 Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, a written explanation will be included to detail why the data was not recorded. If the item is not applicable to the individual case, a notation will be made. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered closely to the original data. All such changes will be initialed and dated. There will be no erasures or white-out on CRFs. For clarification of illegible or uncertain entries, the clarification will be printed near the item, then initialed and dated. Electronic CRFs in the REDcap system will include an audit trail.

The CRFs that will be used in this study are:
Demographics
Concomitant Medications
Adverse Events
Birth Control Assessment
Urine Drug Screening
Vital Signs
Blood Alcohol Level
Time-line Follow-back
Pregnancy test
Birth control assessment
Medical History
Physical Examination

MINI diagnoses summary
Medication Compliance log
Eligibility
ECG
C-SSRS
CIWA-AR

11.4 Study Records Retention

Study records will be retained for at least seven years after completion of the study.

12 Statistical Plan

12.1 Study Hypotheses and Planned Analyses

Calibration Phase I

The objective of the Phase 1 of this study is to use data obtained from subjects who have consumed alcohol in a controlled laboratory setting to develop a model of the relationship between BrAc and TAC measurements that will allow for the determination of estimated blood alcohol levels (BAL) from TAC data collected over extended periods of time.

The results of several studies support the expectation that for most subjects the time to reach peaked alcohol concentrations (Tmax) will be greater for TAC as compared BrAc values [20-21]. In contrast, maximal BrAc concentration (Cmax) values are expected to be smaller be for TAC values collected during test session as compared to those obtained for BrAC measurements. Nevertheless, if TAC values detected by the test device are a directly related to blood alcohol levels there should be will be a strong correlation between the CMax for both TAC and BrAc measurements. Therefore, we hypothesize that for correlations between Cmax values for TAC and BrAc values should be have an r value of 0.8 or greater. A finding consistent with this hypothesis will provide evidence that the test alcohol monitor is able to detect TAC levels that are directly related to BAL.

Validation Phase

Validation Phase

TAC data collected during validation phase will be converted into predicted BAL values for individual subjects using the models developed in the Phase 1 of this investigation. Data obtained during the validation phase will be inspected to determine if there are differences in the sensitivity between the breathalyzer and the wristwatch sensor. Time concentration curves for BrAc and predicted BAL values will be produced for each subject. These curves will be examined to check whether there are any systematic differences between these two measures in the time needed to reach maximal concentration levels for each of the subjects (Tmax) and between the values obtained at the maximum concentration levels (Cmax). .

Predicted BAL that will be determined from TAC data are expected to be equivalent to BrAc concentrations. We, therefore hypothesize that there will be a strong correlation between BAL and BrAc measurements obtained at the same time points for the individual subjects. The reference breathalyzer response is known to be linear over the range of expected blood alcohol levels in the study [23]. Therefore, the breathalyzer and predicted BAL values are expected to be linearly related to each other. To confirm the hypothesis that these values are highly linearly related an analysis will be conducted in which repeated measures correlation coefficient (rcmm)] between BrAc and BAL will be obtained. In contrast to a simple correlation analysis of data in which repeated measures collected from individual subjects are used, here will be no violation of the assumption of independence of observations when rcmm values are utilized as the measure of the extent of correlation between these values [Bakdash and Marrusich, 2017].

Data obtained in the validation phase of this study will be analyzed using the proc glm procedure for SAS 9.4. This data will include values for individual subjects obtained for each time-point at which BrAc measurement were made and corresponding predicted BAL values determined for these subjects. This data will be analyzed using following general linear model:

BAL= BrAc sub

This model is equivalent to an analysis of covariance model in which subjects (sub) are a covariate. This model will allow for the determination of whether BrAc and BAL values are significantly related to one another. The correlation coefficient [rcmm] for relationship between BAL and BrAc will be determined using the following equation first mentioned by Bland and Altman [24] with sum of squares values being obtained from the results of our glm analysis:

rcmm= square root [Sum of Squares BAL/ (Sum of Squares BAL + Sum of Squares Residual)]

Since both BrAc and BAL measurements are hypothesized to be linear, the rcmm value is expected to be >0.80 with high correlation power. The statistical null hypothesis is that the predicted BAL measurements are not related to the standard breathalyzer measurements. The study is designed to maintain a probability of Type I and Type II error rates with respect to the null hypothesis at $p<0.05$.

Given that BAL and BrAc are expected to equivalent it is also hypothesized that there will be a strong correlation between Cmax and Tmax values. Pearson correlation coefficients for correlation analysis between both Cmax and Tmax determined from individual subjects' BrAc and BAL curves, therefore, are expected to be 0.8 or greater, with p values being less than 0. 05.

Hypothesis	**Planned Analyses**
1. There will be a significant correlation between BrAc predicted BAL measures	Repeated measures correlation analysis of wristwatch TAC measurements and contemporaneous BAC measurements from breathalyzer.
2. There will be a significant correlation between Cmax and Tmaxalues obtained for paired BrAc and predicted BAL measurements.	Pearson correlation analysis for Tmax and Cmax values obtained for BrAc and predicted BAL data.

We expect that the results of this study will demonstrate the effectiveness of the developmental wristwatch transdermal alcohol sensor. Furthermore, these results and the developmental work to calibrate this wristwatch will contribute significant knowledge toward the understanding of reliable measurement of blood alcohol via transdermal routes.

12.2 Sample Size Determination

Power analysis: Eight concurrent readings of breathe (BAL) and transdermal alcohol concentration (TAC) will be obtained from the wristwatch sensor and the breathalyzer starting 15 minutes after the start of subject alcohol consumption to the end of the 60 minute drinking session. An additional 20 concurrent readings will be collected during the 5 hour observation period in phase I, and an additional 12 concurrent readings in the 3-hour observation period in phase II. This means that a possible 28 (Phase I) or 20 (phase II) points may be available for this analysis if only pairs of data are used for which values for both devices exceed zero. However, the sensitivity of the wristwatch sensor in human subjects is currently unknown, and so fewer than 20 data points may be of use for our analysis.

Data will be analyzed using a repeated measures correlation (rcmm) procedure described by Bland and Altman [24] and Bakdash and Marisich [25]. For the wristwatch device to be considered to be useful the r value for the correction between BrAc and predicted BAL measures must exceed 0.9. Cohen [26] defines a large effect size as being r=0.5. Bakdash and Marish provide power curves for the rcmm procedure. These curves indicate that for a large effect size (r=0.5) that the power approach 99% when data from only 10 points are available for sample size of about 7. We anticipate a repeated measures correlation value of at least 0.8 and hope to observe a correlation of 0.9. Bakdash and Marisich [25] indicate the degrees of freedom for determining rcm values can be determined using the following equation:

Df= (Number of subjects-2) x (number of data points -1).

The degrees of freedom can be used to determine the corresponding sample size, with the degrees of freedom for standard tables of power analysis being equal to N-2 (Df=N-2). Using this relationship we use the Proc Power procedure for Pearson correlations in SAS to determine the power for 21 data points collected for 9 subjects and 10 datapoints for 5 subjects. In both of these analyses the calculated power value was > 0.995 for rcm of 0.8 or 0.9.

If the existence of a time lag is found that precludes the usefulness of rcm values then Pearson correlations will be determined for AUC and Cmax values. For both of these value obtained for the TAC-BAL data for r=0.8, power will equal 0.82 for a sample size of 9 subjects who complete Phase I and Phase II. We anticipate consenting 36 subjects to achieve a sample size 12 randomizers and 9 completers.

Given that this is a laboratory-based experiment we do not plan to conduct any planned interim analyses in this study.

13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the

IRB concerning the conduct of the study will be made in writing to the investigator. A copy of the initial IRB approval letter will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

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15. Appendix A: Schedule of Events

	Baseline	**Phase I Calibration session**	**Phase II eligibility determination**	**Phase II Validation session**
Clinic Visit #	**1**	**2**	3	**4**
Informed Consent	**X**			
Locator Form	**X**			
Demographics	**X**			
Medical History	**X**		**X**[1]	
Physical Exam	**X**			
MINI V 6.0	**X**			
Clinical labs AST, ALT	**X**		**X**	
Urine Drug Screen opioids, cocaine, amphetamines, methamphetamine, tetrahydrocannabinol (THC), barbiturates, oxycodone, buprenorphine, methadone and benzodiazepines	**X**	**X**	**X**	**X**
Vital Signs, weight, Blood Alcohol Level	**X**	**X**	**X**	**X**
ECG	**X**			
Prior and Concomitant Meds	**X**	**X**	**X**	**X**
CIWA-AR	**X**	**X**	**X**	**X**
Eligibility Checklist	**X**	**X**	**X**	**X**
Urine Pregnancy Test	**X**	**X**	**X**	**X**
Birth control assessment	**X**	**X**	**X**	**X**
AEs	**X**	**X**	**X**	**X**

C-SSRS	**X**		**X**	
Alcohol Education				**X**
TLFB (28 day at baseline phase II eligibility visits)	**X**	**X**	**X**	**X**