Alcohol Biosensor Monitoring for Alcohol Related Liver Disease

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Study Protocol and Statistical Analysis Plan

A. Specific Aims - Alcohol Biosensor Monitoring for Alcohol Related Liver Disease

Successful treatment of alcoholic liver disease (ALD) depends primarily on total abstinence from alcohol. Patients are instructed to maintain complete abstinence in order to have the best health outcomes and prevent ALD sequela or worsening of their liver disease. Different than addiction treatment where abstinence or even harm reduction may be an eventual goal with less need for immediate adherence, the complete abstinence requirement in this patient population makes it a useful model in which to test new strategies for efficient monitoring of patient behavior. Currently monitoring of ALD patients' alcohol use is primarily done through clinical interview and conventional laboratory alcohol testing. Optimally patients would be interviewed frequently and randomly tested, although in real world clinical settings this is difficult to accomplish. Continuous monitoring of alcohol use by wearable biosensors is possible but to date these devices have not been used in clinical medical settings to monitor adherence to medical directives. For ALD patients such devices could facilitate monitoring of alcohol abstinence providing both patients and clinicians with real-time information that may be critical for development and adjustment alcohol treatment plans.

From our prior work (K23 AA00257 and R01 DK066266) we determined that most discoveries of alcohol use in ALD patients are not made until months after the initiation of consumption and were largely captured based on prospective repeated multi-method research measures not routinely employed in a clinical setting. Continuous alcohol monitoring in the months following a hospitalization for ALD could provide more accurate appraisal of alcohol use that when combined with feedback may motivate patients to change drinking habits and engage in appropriate treatment intervention. Whether biosensor devices would facilitate identification beyond self-reports, be integrated into the clinical workflow, accepted by clinicians and patients, and improve outcomes requires investigation. Recent technology advancements expand continuous biosensor performance while reducing overall cost. It could be assumed that monitoring with a biosensor would be more convenient and more desirable, but there could be disadvantages. Patients may feel uncomfortable using the device or feel it is an intrusion. Clinicians may find additional data cumbersome or not useful to care delivery.

Therefore feasibility of integrating such technology into routine clinical care requires examining both patients' and clinicians' perceived potential benefits (e.g., patient convenience, clinician confidence in data and its value, potential improvement in care delivery, facilitation of developing/adjusting treatment plans, reduction in staff burden) and possible barriers (e.g. patient resistance to adoption, disruption of clinician workflow or established communication). These process considerations are essential to guide the development of a full scale trial and future translation into clinical practice. Thus the convenience, feasibility and acceptability of such devices require vetting by patients and clinicians alike. Our R21 proposal targets NIAAA PA 15-301 Alcohol Use Disorders: Behavioral Treatment, Services and Recovery Research soliciting proposals for co-morbid medical and alcohol use disorders, specifically proposals using technology to develop and validate assessments capturing real-time data to use in clinical treatment paradigms.

We propose a 3 month RCT pilot of alcohol biosensor monitoring (ABM)(WrisTAS-see methods) for patients with a recent hospital discharge for ALD decompensation. Patients who intend to stop drinking will wear the ABM and be randomized to receive ABM personalized feedback on the data retrieved from the device (ABM) vs. an enhanced usual care group that will wear the ABM device but not receive information about device data (EUC). Considering future translation into medical practice we chose a monthly assessment schedule aligned with the typical ALD clinical follow up and chose the EUC group to most closely resemble a typical medical encounter where generic questions on alcohol use are asked. The study will also include quantitative and qualitative data collected from participants and 15 clinical stakeholders (e.g. physicians, nurse practitioners, care coordinators) who will provide opinions on ABM usability, acceptability, feasibility*, and potential to change clinical care and outcomes.* Qualitative methods are especially useful for understanding patient and clinician cultures and perspectives to determine the perceived needs, barriers, and preferences for monitoring alcohol use and are essential for future translation of this technology into clinical practice.

Specific Aim 1. To determine usability, acceptability, feasibility and efficiency of ABM for ALD patients.

Specific Aim 2. To determine whether ABM plus feedback improves outcomes for ALD patients who intend to stop alcohol use compared to EUC. Hypotheses 1-5: ABM will 1) reduce alcohol use (primary outcome), and 2) improve readiness for alcohol abstinence, 3) improve self-efficacy, 4) improve initiation of addiction treatment and 5) reduce ALD related hospital admissions and ER visits (secondary outcomes).

Specific Aim 3. To explore with clinicians whether ABM data is useful, acceptable, feasible and efficient.

This study will inform our development of a full scale project by 1) determining the *potential for and value to ABM healthcare integration* 2) identifying barriers to ABM implementation 3) determining long term wearability of ABM devices and 4) determine whether identified patient outcome effect sizes appear clinically meaningful to justify ABM monitoring and evaluation in a full-scale randomized controlled trial in the clinical environment.

D. Approach: Research Design and Methods

We address the NIH mandate for rigor and transparency (NOT-OD-16-011) in the proposal and Table1. **Sample:** We have an ample study population*. In the past 15 months >600 ALD patients were treated at the UPMC Center for Liver Diseases (CLD); >130 discharged from an ALD decompensated hospitalization who lived ~30 miles of our clinic. Such patients require close CLD follow up for medical care, typically monthly after hospitalization*. Our center's ALD population is comparable to regional and national data *not only for gender and age, but race/ethnicity as well*, aiding generalizability. We will recruit for 15 months with planned 4-5 enrollees/month. *We have had good recruitment (<10% refusals) and retention (80-90%) for prior ALD cohorts and Drs. Dunn and Jakicic have had ≥75% consistent wearing of biosensors in prior studies.[47,54] If required to assure assessments' completion we will ask participants to return for a study visit or make home visits.*

Recruitment: Patient Participants-Patients followed at the CLD clinic who are hospitalized for decompensated ALD will be approached for recruitment before discharge. In keeping with NIAAA initiatives for data harmonization we use NIAAA alcoholic hepatitis consortium definitions for alcohol consumption history, liver disease diagnosis, and associated liver enzyme profile.[55] Patients must have a history of excessive alcohol consumption based on quantity/frequency/duration defined as ≥ 40 grams of ethanol per day for women or ≥ 60 grams ethanol per day for men[56] for six months or more.[55] Patients can be drinking up to admission but not have sustained sobriety (>3 months). Diagnosis of decompensated ALD will be established by a CLD hepatologist as defined above.[2-4] Patients may have hepatitis C for which curative therapies exist. **Clinician participants**-15 CLD clinicians caring for ALD patients will be recruited to participate in Aim 3 qualitative and quantitative interviews. Clinicians will be selected from a pool of 25 CLD hepatologists, certified clinical nurses, and nurse practitioners (ages 27-70, all > 5 years practice, 50% female).

Table 1. Scientific Rigor, Reproducibility & Transparency Study Plans

- Scientific premise based on prevalence of ALD and need for novel strategies to address ALD alcohol use
- Enhanced reproducibility by harmonizing with NIAAA initiatives for standard definitions and common data elements for clinical trials by:
  - -Using NIAAA Project Match outcomes instruments
  - -Using NIAAA alcoholic hepatitis consortium definition of sufficient alcohol exposure, baseline data, outcomes
- Recruitment efforts to ensure sex distribution as in ALD
- Well-designed data safety & monitoring plan (sect 4.1.)
- Registering on ClinicalTrials.gov
- Resource sharing plan for NIH/qualified investigators
- CONSORT Guidelines in reporting the study findings

Screening: Patients with ALD will be asked if they intend to stop drinking/remain abstinent and if so will be screened for recruitment. Patients will be screened using 7 items on the recognition subscale of the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES V.8)[57] and the Montreal Cognitive Assessment (MOCA)[58] to screen for cognitive impairment. Patients will be asked about current other drug use.

Inclusion: ≥ 18 years old, willing to accept randomization, and agree to wear device for 3 months. Consistent with findings from alcohol treatment seeking individuals in NIAAA's Project MATCH[59] we will enroll ALD patients with SOCRATES problem recognition subscale score >26 (scores ≤26 indicate very low recognition). Maisto[60] suggests individuals with low recognition in the face of secondary alcohol complications may have pathological denial or cognitive impairment and these individuals are unlikely to intend to stop use.

Table 2. STUDY PROCEDURES

Recruitment, screening

- Prior to discharge from ALD hospitalization patients will be approached by CLD staff
- After CLD staff receive verbal consent, study coordinator will contact and screen patients (SOCRATES recognition subscale >26). If subject meets screening criteria they will be consented and enrolled

***Randomization* and baseline assessment**

- *Subjects will be randomly assigned 1:1 ratio ABM with feedback or EUC (permuted blocks to limit assignment imbalances across enrollment). All subjects wear ABM (WrisTAS)*
- *Random assignment implemented using sequential, opaque, numbered envelopes opened by the study coordinator who will inform the subject. Investigators/assessors blinded to allocation*
- Baseline assessments completed–Form90 AI, SOCRATES, AASE, AWR, DrInC, DPI (Table 3)

***Monthly ABM feedback and EUC procedures* (see Appendix A) and data collection (Table 3)**

- ABM –receives monthly typical CLD medical appointment clinic questions plus personalized feedback on downloaded ABM drinking data, risk/referral information, and patient brochures if alcohol use reported
- EUC –(attention control) monthly typical CLD medical appointment clinic questions including self-report alcohol questions, risk/referral information and patient brochure provided if alcohol use reported
- Issues with comfort or adjustment of WrisTAS will be addressed
- *See methods & 4.1.5.data safety monitoring for quality control procedures monitoring intervention fidelity*
- 6 week mid-point assessment on study outcomes-Form90 AI, SOCRATES, AASE, AWR, DrInC, DPI

Final Assessment procedures

- Repeat of baseline measures–Form90AF, SOCRATES, AASE, AWR, DrInC, DPI (Table 3), TAM2
- Qualitative interview on feasibility, acceptability usability (Appendix B)
- 15 CLD clinicians complete TAM2 and INT questionnaires and have qualitative interview on feasibility, acceptability, usability, *applicability to health care* (Appendix B)

Exclusions: Non-English speaking (<5% CLD); persisting encephalopathy, MOCA scores <21 (moderate cognitive impairment) or neurologic diseases (e.g. Parkinson's), conditions which would affect survey assessments; patients with unresponsive acute alcoholic hepatitis, multi-organ failure, fulminant hepatic failure, or MELD score >21(all with 3-month mortality ≥20%),[61,62] cancer/terminal illness, non-cirrhotic conditions; those unable to wear a wrist monitor (e.g., edema); and *those currently abusing drugs (checked by urine toxicology screen),* lacking a residence, or unable to identify a contact person (if lost to follow-up).

Study design/methods for patient: (*see Table 2 procedures*): We will screen and enroll using above inclusion/exclusion criteria. We will

demonstrate the ABM device and note it must be worn at all times. We will use a 2-arm parallel groups design; subjects randomized 1:1 to either receive personalized feedback on the ABM data or receive enhanced usual care (EUC). The EUC group will have ABM data down-loaded for alcohol outcomes assessment but will not receive feedback on the data. *At each of 3 consecutive monthly sessions both groups* will be asked standard medical questions (e.g. medications, symptoms). In addition the ABM feedback group will receive personalized feedback on downloaded data including graphical displays of alcohol use (Appendix A). Our feedback script is based on standard personalized feedback interventions using key elements: personalized alcohol use information, comparison to normative cohort, risks of use, and resources for help.[52,63,64] At the first visit (and at subsequent visits if use continues) both groups will receive information on negative health consequences, local alcohol addiction treatment referral information, and 2 NIAAA brochures on health consequences and treatment help (see scripted protocols Appendix A). EUC is "enhanced" because beyond generic alcohol use questions scripted information on risks and resources is not commonly provided. A research assistant blinded to assignment will perform outcome assessments at baseline, 6 weeks and final interview. Final assessments include quantitative and qualitative questions on perceived usability and device satisfaction, acceptability, lifestyle compatibility, and feasibility of long term use. So as not to pair participant payment with intervention, the payment schedule aligns with assessments but includes compensation for wearing the device.

For ultimate medical setting dissemination we use non-physician personnel because we see this as the future of such interventions. Medical technicians, increasingly used to extend clinical staff, are ideal for feedback delivery. *Our study uses medical technicians who will be assigned to only one arm of the study and separately trained to prevent cross-contamination. Drs. DiMartini and Dew will train them on protocol delivery using lectures, role playing, audiotaping and training cases using the designed feedback delivery sheet/printed materials provided to participants. During training we will elicit and address any challenges to the maintenance of fidelity. Dr. DiMartini will assess competence based on ratings following principles of treatment fidelity evaluation,[65,66,67,68] to focus on adherence and competence to the structured, didactic style of sessions. To maintain session and assessment fidelity refresher training will occur midway through the enrollment period, and adherence, competence and reliability will be rated. For certification a random 20% of audiotaped sessions will be reviewed with retraining for deficiencies (see also DSMP 4.1.5.a Fidelity Development, Training, and Monitoring). Completed assessment and feedback sheets will be inspected for errors.*

Clinician participants: At study completion 15 CLD clinicians will review de-identified ABM data from the study and be asked a range of quantitative/qualitative questions on feasibility, acceptability, usability, graphical display of data, workflow integration, *and potential health impacts* (Appendix B) and be paid.

E. Analytic Plan

Specific Aims 1 & 3. To determine usability, acceptability, feasibility and efficiency of ABM for patients and clinicians. **Qualitative data coding and analysis:** De-identified transcribed interviews will be thematically coded[107] and a codebook developed for patients and clinicians. The constant comparison method will be used, and subsequent interviews may be modified/informed by findings from previous interviews to explore emerging themes as analysis proceeds. After initial consensus is reached among two coders, interviews will be coded by one coder and reviewed by at least one additional coder. Coding discrepancies will be resolved through consensus. Periodic interviews (expected rate, 1 in 8) will be coded by two coders independently as another check for inter-coder reliability. Further, interviews that have already been coded will be reviewed as more codes are identified. Dr. Dew will monitor for coding drift by periodically contrasting recent vs. earlier coded interviews. For ***SA1&3*** a summary of themes extracted from patient and clinician interviews will be prepared, with examples of interview quotes. We will also examine descriptive statistics on WrisTAS data including amount of time worn vs. removed and examine data for evidence of tampering to use as variable examining wearability and feasibility.

Specific Aim 2. Analyses will follow an intent-to-treat principal. We will first examine univariate distributions on baseline characteristics and on each outcome. We will examine the data for extent and pattern of missingness across outcome assessments. Potential violations of assumptions of planned parametric methods of analysis will be explored and resolved, e.g., variables will be transformed as needed; nonparametric methods will be employed if transformations are inadequate. Baseline demographic and clinical characteristics of the two study groups will be examined via x^2 tests for categorical variables and t-tests for continuous variables (or Wilcoxon Rank Sum tests if necessary) in order to (a) describe the sample and (b) evaluate whether the randomization process effectively balanced the groups. If imbalances are observed, we

may need to adjust (covary) for significant and/or large baseline differences in the evaluation of hypotheses.

The primary outcome is alcohol use (H1), which we will test via 2 measures: % of days drinking; total quantity/frequency during period between downloads. Secondary outcomes (***H2-4)*** are readiness for alcohol abstinence, self-efficacy, initiation with addiction treatment will be analyzed using SOCRATES subscales and AASE/AWR (continuous variables), ***H5*** Form 90AF hospital stays and ER visits (% of days hospitalized and no. of hospital admissions+ER visits). For each primary/secondary outcome, we will use a linear mixed effects model with fixed effects for intervention group (2 groups) and the repeated measures factor, time (pre-intervention, 6 weeks, and 3 mons post-intervention); and random effects for individual participant and intercept.

Statistical Power: Ours is an exploratory study; the ESs we might observe are unknown. For the simple effects we will compute as described above, with 30 participants in each of 2 groups being compared in a given test and alpha at .05, we would have power at 80% to detect an ES, d$\geq$0.76. Brief feedback interventions can produce moderate to large ESs for reducing alcohol use and consequences (d of 0.6-0.8).[81,111-113] Even if 5-8 participants are lost to attrition, we should have sufficient power to detect simple effects within the range found in previous feedback studies. Again, however, our interest will be to examine feasibility issues and ESs as opposed to testing for statistical significance.