PROTOCOL TITLE:

Team Science to Identify and Intervene on Metabolism- and Alcohol-Associated Liver Disease (MetALD)

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1.0 Study Summary

Protocol Information	Description
Study Title	Team Science to Identify and Intervene on Metabolism- and Alcohol-Associated Liver Disease (MetALD)
Study Design	The research design is a mixed-methods randomized controlled trial (RCT) comparing standard and enhanced approaches to screening, brief intervention, and referral to treatment (SBIRT/P) for metabolism- and alcohol-associated liver disease (MetALD). Adults age 21+ with indicated risks for MetALD based on alcohol intake and body mass index (BMI) and who speak Spanish or English are offered free, confidential liver screening with Fibroscan®, a noninvasive, painless ultrasound to measure stiffness and fat in the liver. Procedures include a prescreening survey, in-person screening, a randomization visit, and a ~30-day followup visit. At the end of the randomization visit, participants receive a brief intervention to increase motivation for healthy lifestyle which includes either integrated Fibroscan® results or standard health information. At the end of the followup visit, participants complete exit interviews to obtain qualitative data to supplement quantitative indices of feasibility, acceptability, and small-scale effectiveness.
Primary Objective	The primary aim of the research is to show that SBIRT/P can be optimized by integrating results of noninvasive Fibroscan® liver screening for adults age 21+ from underresourced communities and with behavioral risks for MetALD.
Secondary Objective(s)	Secondary aims are to evaluate the precision of biobehavioral endpoints for alcohol intake, weight-related behaviors, and cardiometabolic health, and to explore plasma biomarkers to indicate likely steatosis and fibrosis, with Fibroscan® as a reference standard.
Research Intervention(s)/ Investigational Agent(s)	All participants receive SBIRT/P including a brief intervention to increase motivation for healthy lifestyle, toward the end goal of reducing risk of multiple chronic conditions, including MetALD. In the standard SBIRT/P condition, the brief intervention includes standard health information. In the enhanced SBIRT/P condition, results of noninvasive Fibroscan® liver screening and staging are integrated to optimize intervention benefit.
IND/IDE #	NA
Study Population	Adults 21 years of age or older with concurrent risk factors for MetALD based on alcohol intake and body mass index and who speak Spanish or English.
Sample Size	The target number of participants to be randomized is 40 (20 per condition). An estimated 80 potential participants will complete informed consent prior to in-person screening to confirm eligibility, allowing for screen failures and disinterest.

Study Duration for individual participants	Eligible participants are scheduled for a randomization visit, typically within 5 to 10 business days of in-person screening. Approximately 30 days after the randomization visit, participants return for a followup visit to repeat measures and assess satisfaction with SBIRT/P. The total study duration is typically 45 days or less, with flexibility to accommodate schedules.
Study Specific Abbreviations/ Definitions	Alcohol-associated liver disease (ALD) Alcohol use disorder (AUD) Body mass index (BMI) Metabolic dysfunction-associated steatotic liver disease (MASLD) Metabolism- and alcohol-associated liver disease (MetALD) Motivational Interviewing Treatment Integrity (MITI) Randomized controlled trial (RCT) Screening, brief intervention, and referral to treatment (SBIRT/P) Vibration controlled transient elastography (VCTE)

2.0 Objectives

2.1 The purpose of this randomized controlled trial (RCT) is to test whether screening, brief intervention, and referral to treatment and prevention (SBIRT/P) is improved by integrating results of noninvasive liver imaging with Fibroscan® for adults age 21+ from underresourced communities who speak English or Spanish and are at risk for metabolism- and alcohol-associated liver disease (MetALD).

2.2 This research aims to demonstrate that SBIRT/P is an effective way to identify and intervene for MetALD in underresourced communities. Identifying individuals with alcohol intake and overweight-related risks for MetALD and engaging them in brief intervention to promote healthy lifestyle can reduce risk of multiple chronic diseases, including MetALD. We hypothesize that integrating results of noninvasive liver screening and staging with Fibroscan® liver imaging will enhance the effectiveness of a brief intervention to promote liver and heart health, as compared to a brief intervention with standard health information.

3.0 Background

3.1 Chronic, steatotic liver disease is a leading cause of death in the United States (US) and worldwide. As alcohol intake and obesity rates remain high and rising, and the population of adults in the US who are at risk for irreversible liver damage and cardiometabolic health problems is substantial, particularly among underresourced communities. Updated nomenclature and criteria provide a standardized, inclusive, and nonstigmatizing framework to identify adults at risk for or with steatotic liver disease. In addition to metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD), a concurrent-etiology type, metabolism and alcohol-associated liver disease (MetALD), identifies those whose drinking may not have yet progressed to the levels seen for patients with ALD but who have an additional cardiometabolic risk factor for chronic steatotic liver disease.

3.2 Observational data show that obesity worsens ALD severity, and any drinking accelerates MASLD. Yet, there is currently no preventative interventions or medical treatments to simultaneously address weight-related behaviors and alcohol use to decrease risk for progressive liver damage from both etiologies in MetALD. Importantly, liver disease from alcohol intake and metabolic etiologies is preventable and treatable only through lifestyle changes. Our preliminary data from patients with alcohol use disorder (AUD) and at-risk for or with ALD demonstrated feasibility and acceptability of a brief motivational intervention to reduce alcohol consumption, delivered in English and Spanish for adults recruited from specialty liver clinics and remotely from the community.

3.3 Whereas liver-related deaths due to viral infection have declined sharply in recent years through groundbreaking treatments, mortality rates for liver diseases related to alcohol intake and obesity have risen. If left unaddressed, MetALD mortality rates are projected to double by 2040. Research to develop effective strategies to identify and intervene for MetALD in underresourced communities is essential and has potential to help many people avoid irreversible liver damage. Screening, brief

intervention, and referral to treatment/prevention (SBIRT/P) is an effective way to promote liver health and avoid irreversible damage. Interventions to reduce alcohol intake and weight-related behaviors, such as high-fat diet and sedentary lifestyle, are efficacious when delivered, but as many as 90% of those who need intervention are not being reached. In Latinx communities, lack of societal privilege and language barriers can intensify disparities in access to alcohol services, weight management, and linkage to liver care, with deadly and costly outcomes. SBIRT/P integrated at the point of care is a promising strategy to reach people at risk for MetALD, avoid progressive liver damage, and address socioeconomic barriers in communities experiencing health disparities.

4.0 Study Endpoints

4.1 Primary endpoints include: (a) proportion screened who have alcohol intake and weight-related risks for MetALD; (b) proportion eligible and invited to participate who agree to noninvasive liver imaging with Fibroscan® and arrive for their scheduled appointment; (c) satisfaction with Fibroscan® liver screening; and (d) acceptability metrics for SBIRT/P overall, including retention rates and satisfaction ratings compared across randomized conditions. Satisfaction with Fibroscan liver screening is assessed with a single-item visual analog scale with 0 indicating low satisfaction and 100 indicating high satisfaction. Satisfaction with SBIRT/P overall is assessed with the Client Satisfaction Questionnaire, provided in an attachment.

4.2 Secondary endpoints include: (a) self-reported drinking quantity and frequency (e.g., heavy drinking days, drinks per week, alcohol-free days); (b) phosphatidylethanol (PEth), a direct alcohol metabolite biomarker; (c) self-reported weight-related behaviors (e.g., diet quality, eating dysregulation, food cravings, and physical activity); and (d) weight-related biometrics (e.g., body weight, waist circumference, blood pressure). Descriptions and items for secondary-endpoint measures are provided in an attachment. Measures to describe the sample participating in this research, to account for important covariates, and to facilitate team science are also attached. The battery of measures is streamlined from prior projects to reduce staff time, minimize participant burden, and facilitate remote data collection.

4.3 Exploratory endpoints include plasma biomarkers to comprise a preliminary panel to screen for likely steatosis and fibrosis in patients at risk for MetALD, with Fibroscan® as a reference standard. These include plasma biomarkers of microbial translocation, innate immune activation, obesity-related metabolic dysfunction, and liver fibrosis.

5.0 Study Intervention/Investigational Agent

5.1 In the standard SBIRT/P condition: Information about the participant's alcohol- and weight-related risk factors for MetALD is provided. The information includes comparison of the participant's health metrics with public-health guidelines.

5.2 In the enhanced SBIRT/P condition: Results of noninvasive liver imaging and staging via Fibroscan® is integrated into the brief behavioral intervention to enhance motivation for healthy lifestyle behaviors, reduce

risk of multiple chronic diseases including MetALD, and promote overall health and wellness. The information includes interpretation of the participant's Fibroscan® steatosis and liver stiffness measurements based on MetALD diagnostic criteria and published liver-health guidelines.

5.3 Randomized conditions include either standard or enhanced health information in the setting of evidence-based, motivational interviewing (MI). A treatment manual has been cultivated over decades of research by this team and multiple prior clinical research protocols including our recent study of brief MI for AUD and ALD. The intervention has the potential to have high impact on the dual etiologies of MetALD, i.e., alcohol consumption and weight-related behaviors.

5.4 N/A. IND/IDE are not applicable. The Fibroscan® is a well-established research and clinical screening tool for steatosis and fibrosis. Fibroscan® is the gold standard procedure for obtaining information on liver health and is the primary noninvasive diagnostic screening method used in research and clinical practice prior to an invasive liver biopsy.

5.5 Fidelity (adherence) monitoring via Motivational Interviewing Treatment Integrity coding system (MITI Coding Manual 4.1; Moyers, Manual, & Ernst, 2014) will evaluate the degree to which the intervention is delivered by the interventionist(s) as intended with consistency across randomized groups and facilitate supervision of the intervention by a licensed clinical psychologist or other licensed practitioner in Rhode Island.

6.0 Procedures Involved

6.1 Study procedures described herein do not involve more than minimal risk. The research design is a mixed-methods RCT comparing standard and enhanced approaches to SBIRT/P for MetALD. The research, including all procedures and materials, is implemented in English and Spanish. Any modifications of study procedures described herein will be reviewed and approved by the Brown University IRB. The addition of key personnel will be submitted to the IRB and appended to the IRB record upon administrative review. All personnel will have documented human subjects research training prior to engaging in research activities.

6.2 This study builds upon prior research through partnering with Clínica Esperanza/Hope Clinic (CEHC) to address issues of low and inequitable access to alcohol health services and liver specialty services across the care continuum. CEHC is the primary site for recruitment and data collection, and established partnerships with Brown Medicine primary care clinics can supplement to meet enrollment targets. The section on recruitment methods provides information to describe recruitment procedures and participant compensation.

6.3 Interested volunteers complete a brief, confidential pre-screening survey to assess eligibility and provide basic demographic information to describe the sample of potential participants reached for screening by these procedures. The pre-screening survey questions to assess eligibility and an accompanying script are provided in an attachment. Responses to the pre-screening survey are recorded via Brown-approved, HIPAA-compliant survey software for the purpose of tracking reasons for ineligibility.

Personally identifiable contact information will be securely stored using HIPAA-compliant software vetted and approved by Brown CIS. After pre-screening in partnering clinics or over the phone, a community health worker (e.g., patient navigator or Navegante) or Brown University staff member approaches the potential participant in the clinic or schedules them for an appointment where procedures and risks are explained in person and supplemented by a bulleted written consent form. The consent section of this protocol describes informed consent procedures, which are always done in person via an interactive conversation and documented in writing. Interested volunteers who would like to participate in screening, appear potentially eligible, and complete informed consent with written documentation continue with screening that day, or, if necessary, are scheduled for a visit as soon as possible. Eligibility criteria assessed include interviews, weight-related biometrics, and blood tests, including tests for Hepatitis B and C which are common exclusionary preexisting liver diseases in this population. Additional measures include culturally validated assessments of diet and lifestyle behaviors, described in attachments.

6.4 Those eligible are scheduled for two appointments: (1) a randomization visit typically completed within 5 to 10 business days of in-person screening, and (2) a followup visit ~30 days later. Attendance at all visits is facilitated by reminders in multimethod formats, including email, text message, phone call, and/or calendar invitations, complying with the participant's preferences. The first visit includes the Fibroscan® liver screening, biobehavioral assessments, interviews, and a brief conversation with our study counselor (~45 minutes to 1 hour) to build motivation for lifestyle change. The followup visit repeats biobehavioral assessments and interviews and includes a brief check-in (~15 minutes) with our study counselor with an exit interview assessing satisfaction with study procedures and barriers to change. The Fibroscan® liver screening is not repeated at followup. For participants who are monolingual Spanish speakers or bilingual and prefer to complete the study in Spanish, all procedures including the brief intervention will be implemented in Spanish by bilingual personnel who are either native Spanish speakers or have documented professional Spanish fluency. The total study duration for individual participants is typically less than 45 days, with some variability to allow for flexibility in scheduling.

6.5 Plain language is used to describe what will happen during the Fibroscan® and the procedures for sharing results. During informed consent, visual aids are used to facilitate patients' understanding of the procedures, and a specific pause point is written into the bulleted consent form to solicit questions. Participants are informed that they may or may not receive their liver scan results from their study counselor and that this is decided randomly, like a coin flip. In the enhanced condition, our study counselor receives the Fibroscan® results and shares these with the participant in the context of the brief motivational interviewing intervention. In the standard condition, the same brief motivational interviewing intervention is implemented but includes standard information on lifestyle behaviors and risks without the specific results of the Fibroscan® examination. In both conditions, the Fibroscan® results are reviewed by our study physician, Kittichai Promrat, MD, who is a Brown-affiliated faculty member and

experienced hepatologist directing the Chapman Street Hepatology Clinic and is chief of gastroenterology at the Providence VAMC. Fibroscan® results can be reviewed remotely via encrypted, HIPAA-compliant communication and software provided by the manufacturer, Echosens, https://www.echosens.com/en-us/. Referrals to primary or specialty care for an evaluation will be facilitated by Dr. Promrat, as appropriate, consistent with best-practice clinical guidelines. There is also an independent medical monitor for this study, Lorenzo Leggio, MD, PhD, an addiction-scientist and hepatologist with extensive experience in this role. Dr. Leggio will review individual serious adverse events as well as cumulative progress reports and make recommendations regarding safety and continuation of the study.

6.6 Sources of research data include (a) self-reported data collected by trained staff via interviews and questionnaires, (b) self-reported data collected via HIPAA-compliant survey tools that have been vetted and approved by Brown CIS, stored on HIPAA-compliant, cloud-based servers, and monitored by staff with up-to-date human subjects training, (c) biological specimens collected, stored, and transported by trained staff, and processed in our Clinical Laboratory Core (CLC) laboratory at Brown University or at HIPAA-compliant clinical laboratories (d) biometrics (e.g., height, weight, blood pressure, waist circumference) collected by research staff using structured protocols, and (e) transient elastography Fibroscan® to obtain Controlled Attenuation Parameter (CAP)TM score and Liver Stiffness Measurement (LSM) by Vibration Controlled Transient Elastography (VCTETM) implemented by trained operators certified by the manufacturer, Echosens, and monitored on site and remotely by our clinical partners, our CLC staff including a study nurse practitioner, our study physician, and an independent medical monitor.

6.7 The primary research site for storage and analysis of biospecimens and other data will be the human laboratory at the Center for Alcohol and Addiction Studies (CAAS) at Brown University, School of Public Health, 121 South Main Street, 4th floor, Providence, RI, 02903. The section on data safety monitoring gives more information.

6.8 Visits are expected to be completed at CEHC at 60 Valley Street in Providence RI, or through Brown Medicine primary care clinics or similar, though the availability of our laboratory offices at 121 S. Main Street, School of Public Health provides additional flexibility in the case of unforeseen interruptions in access to appropriate space and resources to complete the research protocol as described herein.

6.9 Fidelity (adherence) monitoring via Motivational Interviewing Treatment Integrity coding system (MITI Coding Manual 4.1; Moyers, Manual, & Ernst, 2014) will evaluate the degree to which the intervention is delivered by the interventionist(s) as intended with consistency across randomized groups. Global ratings include two relational components, i.e., partnership and empathy, rated from 1 to 5, with 5 indicating better adherence. Technical components, i.e., cultivating change talk and softening sustain talk, will also be given global ratings. Finally, behavior counts will be used in the context of supervision to monitor the interventionist skill level and identify any areas for improvement. This process typically includes coding 10-minute segments of a random selection of sessions. Our goal is to exceed that

standard and code 10-minute segments for all 40 sessions for all 40 randomized participants (i.e., one session per participant). Following best practices, two raters will use the MITI coding system to maximize and assess the reliability of the MITI for assessing intervention integrity, including both relational and technical components. Supervision is implemented via audio recordings of interviews, and an option to opt out of audio recording is included on the bulleted consent form.

6.10 N/A. There are no plans for a long-term followup.

6.11 N/A. The study does not test a Humanitarian Use Device (HUD).

7.0 Data and Specimen Banking

7.1 Data and specimens will be banked for future use. Specimens will be stored at Brown's SPH lab until they are used for research purposes or discarded. The specimens will be accessed by primary members of the research team and core lab staff. Future use may involve sending the specimens to clinical and/or research laboratories outside Brown for the purpose of performing further testing, assays, and similar functions.

7.2 The data to be stored with each specimen include study ID number, date of collection, and visit number, where applicable. No personal identifying information is stored with study specimens under any circumstances.

7.3 The specimens will remain under the control of the researchers and will not be released to outside parties.

8.0 Sharing of Results with Subjects

8.1 The conditions for sharing results with subjects and others is described via an interactive informed consent process including a conversation with a trained research team member supplemented by a bulleted consent form. The bulleted consent form includes a section on “Your Liver Results” which describes procedures for random assignment in plain language. Participants who are not randomly selected to receive their results at the randomization visit in the context of the brief intervention can be given these results at the end of their followup visit upon request. These results are prepared in a report that includes information provided in standard medical practice, such as in a health portal report. Participants are free to share these results with their primary care physician together with a copy of our bulleted consent form which provides information about the study procedures and contact information for the researchers. Participants are told, “…our doctor who specializes in liver health reviews your scan results. If the scan shows cause for concern, we will tell you and give you a copy to give to your doctor. If you do not have a doctor, we can help you find one. If our liver doctor thinks you need to go to a specialty liver clinic, we will help you make an appointment.”

8.2 Trained staff inform potential participants of what will happen if blood tests for Hepatitis B and/or C return positive results. If these tests are positive, the findings will be reported to the Rhode Island Department of Health as required by State law. This information is kept confidential by the Department of Health and is used to track diseases. This information is provided verbally and in writing on the bulleted consent form.

8.3 At the conclusion of this research study, the results will be shared with the clinics and communities who participate. There are opportunities for collaborative dissemination via local, regional, and national presentations, as well as publication in academic journals or other appropriate outlets. Individual names or any other personally identifiable information for participants or those screened for research participation are never included on presentations or publications.

9.0 Study Timelines

9.1 The duration of an individual subject's participation is typically less than 45 days, with flexibility to accommodate scheduling.

9.2 The end date of the 11-month project period is July 31, 2025. The strict timeline for the entire project and period of award is dictated by this supplement funding mechanism as indicated by the National Institutes of General Medical Sciences Funding Opportunity Announcement and our Notice of Grant Award which is provided with this application.

9.3 Given this limited timeline, the funder has required that the IRB approval be reported to the sponsor no later than November 3, 2024. The Notice of Grant Award attached with this application indicates that failure to receive IRB approval by this date could result in suspension and/or termination of the funding for this supplement award.

9.4 Primary analyses are expected to be completed within one year of enrollment of the final participant and within two years after the date of approval for research activities to commence.

10.0 Inclusion and Exclusion Criteria

10.1 Screening procedures, described in the relevant section on recruitment methods, include medical record reviews for alcohol intake and body mass index, as well as age and medical conditions or other conditions which are exclusionary as described below. Prescreening questions and the associated script are provided in an attachment.

10.2 Inclusion Criteria. To be eligible, the interested volunteer MUST meet all the following:

- Be at least 21 years of age.
- Exceed alcohol intake diagnostic guidelines for MetALD.
- Have a Body Mass Index (BMI) >=25 kg/m2.
- Be able to speak and read English or Spanish to provide written informed consent and understand written and oral instructions in English or Spanish.

10.3 Exclusion Criteria. To be eligible, the interested volunteer MUST NOT have any of the following:

- Pre-existing liver disease or hepatocellular carcinoma or prior liver transplant.
- Pre-existing medical conditions that, in the opinion of the investigative team, would interfere with research participation

(e.g., loss of kidney function, uncontrolled infections, multiorgan failure, uncontrolled upper gastrointestinal bleeding, other active malignancies except skin cancer).

- Pre-existing mental health conditions that, in the opinion of the investigative team, would interfere with the ability to provide informed consent and understand written and oral instructions (e.g., hepatic encephalopathy, psychotic disorder diagnosis or symptoms).
- Current pregnancy.
- Be anyone who, based on self-reported withdrawal symptoms and the opinion of the investigative team, could not currently safely be withdrawn from alcohol without medical detoxification.
- Currently receiving formalized psychosocial treatment for an alcohol use or drug problem and/or newly taking medications for an alcohol use or drug problem.
- Currently receiving formalized behavioral weight management treatment and/or currently taking weight loss medications.

10.4 The research study will exclude anyone who is not an adult, pregnant persons, anyone who is determined to be or suspected to be unable to consent for research participation and will not recruit from prison settings.

11.0 Vulnerable Populations

11.1 N/A. The research is not anticipated to involve individuals who are vulnerable to coercion or undue influence or special populations.

12.0 Local Number of Subjects

12.1 This pilot aims to randomize 40 participants to standard (n=20) and enhanced (n=20) conditions, with randomization stratified by relevant study variables.

12.2 It is anticipated that ~80 interested volunteers may complete informed consent prior to in-person screening to confirm eligibility, allowing for ineligibility and disinterest after screening.

13.0 Recruitment Methods

13.1 The primary recruitment location is our nonprofit partnering clinic, Clínica Esperanza/Hope Clinic (CEHC) at 60 Valley Street in Providence, RI. The CEHC mission, patient population, and resources are described below. Potential participants may also be recruited from the community or via digital outreach with prescreening completed by phone or online with Brown-approved survey software. Procedures may also be implemented at our main laboratory at 121 S. Main Street, Providence, RI.

13.2 Patient navigators, i.e., Navegantes, are trained community health workers assisting with patient care and outreach for CEHC. The assistance of Navegantes with participant recruitment and retention is key to the success of this research. Study information will be posted and placed in exam rooms, waiting rooms, check-in/checkout windows, and any other locations

within the clinic or in the surrounding community which prospective participants congregate.

13.3 Review of the electronic health record (EHR) identifies patients age 21+ years with current drinking levels and body mass index (BMI) placing them at risk for downstream health complications including MetALD. EHR reviews involving access to personally identifying information is necessary to complete the research. A waiver of HIPAA consent is requested via Appendix G attached with this protocol. Where medical history is available in the record, obvious exclusions are identified (e.g., current pregnancy, Hepatitis B/C diagnosis, prior liver transplantation; see Inclusion/Exclusion criteria for a full list of exclusionary criteria). Where feasible, brief alcohol screening via the 3-item Alcohol Use Disorder Identification Test-Consumption subscale (AUDIT-C) is included as part of patient care. The AUDIT-C items, description, and references are provided in an attachment. Generally, the higher the AUDIT-C score, the more likely it is that the patient's drinking is affecting their health or safety.

13.4 Patients who may be suitable for the study and who have visits scheduled in advance may be sent a letter informing them that Brown University is recruiting patients in the clinic for a research study. In clinic, patients are invited by their health provider, patient navigator, or Brown University research team member to answer a limited set of prescreening questions to see if the study may be suitable for them. Prescreening questions are in plain language, with many asked in an easy to answer yes/no format. For example, "Are you able to read English or Spanish?" The pre-screening questions and corresponding semi-structured script are provided in an attachment. Potential participants who complete pre-screening may be offered a nominal gift (e.g., a pen, notepad, water bottle) or meal as a gesture of appreciation, consistent with best practices for community engaged research.

13.5 If patients are unable to participate in the prescreening at the time of their clinic appointment, prescreening can be completed over the phone or deferred until their next clinic visit. In this case, permission would be requested to remind the patient of their upcoming appointment by common methods (e.g., phone, mail). Potential participants who hear about the study by word of mouth or advertisements in the community or online may also contact the study team by phone, text, or online to hear more about the study and answer the pre-screening questions. In the case of digital outreach with online prescreening, Brown-approved survey software (e.g., Qualtrics or similar) will be used and will include a study landing page that provides enough information to describe study procedures to allow potential participants to decide about their interest in continuing with prescreening. Questions used for online prescreening are the same as those provided in the attachment for phone prescreening and also include the AUDIT-C 3-item alcohol screening measure.

13.6 Following pre-screening, participants will continue with informed consent for research participation prior to further screening to confirm eligibility. This last stage of screening includes a blood draw for quantification of liver function and cardiometabolic factors using standard clinical liver, metabolic, and lipid panels, HbA1c, and Hep B/C testing if not already performed (see

Exclusion criteria), as well as a timeline followback interview to assess recent alcohol consumption with high precision.

13.7 To facilitate recruitment and retention, a secure (e.g., Filemaker or similar, Brown-approved software tracking system) tracking database is accessible via an internet connection at CEHC and our Brown University laboratory offices. The tracking database separately stores screening and participant information and can automatically generate study milestones, task reminder emails for staff, and follow-up appointment scheduling and reminders. Given that the target patient population may not have regular access to internet, email scheduling and reminders only supplement efforts of the research team to contact participants by phone or via in-person interactions. Close-contact locators (e.g., spouse, adult children age 18+, close friend) will facilitate future contact. Obtaining contact information for close-contact locators is necessary to complete the research as underresourced participants may not have reliable phone service, internet access, or stable home address. Obtaining locator information is standard practice for research studies working with underresourced and marginalized populations. Research team members stay in touch with participants regularly to promote attendance to the study protocol. The CEHC Navegantes will assist with scheduling participant appointments and following participants through the protocol offering support, reminders, and ample opportunities for interfacing with the study team. Together, these procedures maximize recruitment and retention through minimizing missed appointments and attrition.

13.8 All study advertisements and recruitment materials using the Brown University School of Public Health logo are required to have approval, and appropriate approval will be obtained prior to implementation. Brown university guidelines for teaser and print advertisements will be followed. Print advertisements will include all required information and be similar to the one attached.

13.9 Compensation procedures will be described to participants during the informed consent process. Compensation amounts and the timeline for payments is provided in the bulleted consent form attachment. Interested volunteers are provided $30 for in-person screening, paid regardless of eligibility. Participants are paid $150 for the randomization visit and $150 for the followup visit. Total possible compensation is $330. Brown university policies and procedures for applying cash payments will be followed with required documentation. Transportation to study visits can be provided at no cost to the participant through Brown-approved and SPH-approved services (e.g., Lyft concierge), public transportation passes, or similar methods. For procedures where participants must arrive fasting (e.g., no food for 3+ hours for Fibroscan®), a meal will be provided. Meals or snacks may also be provided at recruitment events at partnering clinics or other community sites that are easily accessible to the population served.

14.0 Withdrawal of Subjects

14.1 Anticipated circumstances under which subjects will be withdrawn from the research without their consent include instances of repeated missed appointments, apparent intoxication upon arrival to study visits,

inappropriate behavior of any kind toward staff on our team, or similar circumstances. Participants arriving to appointments intoxicated may be rescheduled or may be terminated from the study, with this decision made by the primary researcher on this protocol.

14.2 Participants who choose to withdraw from the study may do so for any reason without penalty to them and will be paid for their participation to that point. During the informed consent process, the choice of participants to be in research or to stop participating at any time is explained verbally and in written form on a bulleted consent document. It is imperative that patients do not feel pressure to participate and understand the study is voluntary. The participant may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

15.0 Risks to Subjects

15.1 Study procedures pose minimal risks. The bulleted consent form and informed consent process describes foreseeable risks and discomforts to the participations because of being in this study.

15.2 Potential risks to human subjects participating in the proposed research are minimal and include as follows:

- Breach of confidentiality.
- Psychological discomfort from answering questions about lifestyle behaviors such as diet, exercise, and alcohol intake.
- Physical risks associated with blood draw procedures including and not limited to pain or discomfort, venipuncture, or fainting.
- Physical or emotional risks associated with liver screening and receiving liver-health feedback.
- Risk of coercion.

15.3 N/A, procedures which may have unforeseeable risks are not expected.

15.4 N/A, pregnant persons are excluded from the research study.

15.5 N/A, risks to others who are not subjects are not expected.

16.0 Potential Benefits to Subjects

16.1 Free, noninvasive liver screening and brief behavioral intervention has potential to reduce risks of liver biopsy and other invasive assessments or interventions in the context of progressive liver damage, thereby reducing the participant's health risks and discomforts, which is a potential benefit.

16.2 Individual participants are unlikely to have any other direct benefits of being in this study.

17.0 Data Management and Confidentiality

17.1 Plans for analyzing the data will be included on clinicaltrials.gov following established timelines and requirements set by the National Institutes of Health. Piloting procedures in randomized clinical trials serves many valuable functions including gauging feasibility of recruitment, piloting randomization procedures, comparing intervention-specific retention rates,

withdrawal rates including reasons for withdrawal, and intervention-specific fidelity rates. A CONSORT diagram will describe the screening and enrollment process implemented and demonstrate feasibility. To examine the acceptability of SBIRT/P procedures, quantitative and qualitative measures of satisfaction with Fibroscan® screening and of the brief motivational intervention will be analyzed.

17.2 Multiple protections will be implemented to secure the data and minimize risk of breach of confidentiality, including (a) training and authorization of access: limiting access to personally identifiable information to personnel with appropriate and up to date human subjects training who are supervised by the investigative team and reminded to keep information confidential, (b) password protection and encryption: digital and hard-copy data securely in accordance with data integrity standards using Brown CIS-vetted and approved software and servers, (c) physical controls and separating identifiers and data: storing personally identifiable information separately from data or biological specimens in locked locations designated for this purpose and coded with a unique ID number that is not directly associated with the participant (e.g., not a birth date), (d) certificate of confidentiality: explaining during informed consent verbally and in writing that the study has obtained a certificate of confidentiality (CoC) from the National Institutes of Health, as well as informing potential participants verbally and in writing during informed consent about the limitations of confidentiality including the limitations of the CoC and instructing participants to protect their own information.

17.3 Procedures that will be used for quality control of collected data will include working from highly detailed project manuals and standard operating procedures that are followed with line-by-line checks for all procedures. The project coordinator or team member in a similar supervisory role will review hard-copy data for errors and document digitally or in writing that this oversight was conducted including the date and name of the person conducting the check.

17.4 Data and specimens will be banked for future use following best-practice guidelines to ensure integrity and confidentiality of the samples.

- Once collected, specimens will be stored at our designated laboratory space at Brown SPH until they are used for research purposes or discarded.
- The specimens will be accessed by primary members of the research team and core lab staff.
- Future use may involve sending the specimens to clinical and/or research laboratories outside Brown for the purpose of performing further testing, assays, or similar functions.
- The data to be stored with each specimen include study ID number, date of collection, and visit number, where applicable. No personal identifying information is stored with study specimens under any circumstances.
- The specimens will remain under the control of the researchers and will not be released to outside parties.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

18.1 N/A. This section is not required when research does not involve more than minimal risk to participants.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 All interviews, exams, and sessions will be conducted following applicable human subjects research protections privacy standards including conducting these in a manner and space that ensures privacy and confidentiality of information. Private identifiable information associated with research data will be available only to research personnel who have been trained in human subjects' protection guidelines and are certified by the Collaborative Institutional Training Initiative (CITI) as mandated by the Brown University IRB. Deidentified data will be indexed by numeric codes which are sequentially generated numbers that are not derived from private identifiable information.

19.2 CEHC is an active clinic serving uninsured individuals as described in other relevant sections herein. The CEHC employs Patient navigators, i.e., Navegantes, who are trained community health workers assisting with patient care and outreach for CEHC. Navegantes are key to the success of this research, as they are a trustworthy and familiar presence in the clinic. Navegantes will assist with a warm hand-off where applicable, i.e., from clinic staff to research staff. Participants are informed that they have the right to decline to answer a particular question that feels too uncomfortable. By conducting study procedures in a more familiar setting (i.e., CEHC), the goal is to increase participants' comfort and sense of agency.

19.3 The research team will access information about the participant via the medical record, the participant's self-report, biometric measurements, and laboratory and clinical tests collected to complete the study aims. Only primary members of the research team are permitted to access participant research data following the required standards to uphold data integrity.

20.0 Compensation for Research-Related Injury

20.1 N/A. The research does not involve more than minimal risk, and there is not available compensation in the event of research-related injury.

21.0 Economic Burden to Subjects

21.1 N/A. Participants are not expected to be responsible for any costs involved in their participation in the research.

22.0 Consent Process

22.1 The informed consent process will adhere to the procedures described in HRP-090-SOP.

22.2 The process for informing potential participants about the study and obtaining their consent for participation will take place in person in a private space and will be documented in writing using a bulleted consent form that is signed with a digital or wet signature by study participants and witnessed by staff on our team.

22.3 After the procedures are described to the potential participant, they may take time to think it over prior to signing. If the potential participant remains interested after having time to consider the research, we will make them an appointment to continue.

22.4 Ongoing consent is supported through informing participants that participation is voluntary at each study visit.

Non-English Speaking Subjects

- All study procedures may be implemented in either Spanish or English. Prescreening questions include asking whether the potential participant can read Spanish or English. Those who cannot speak either of these languages will not be eligible to complete informed consent for research participation and cannot enroll in this study. Participants must speak, read, and understand, Spanish or English to be eligible.
- For monolingual Spanish speakers, all procedures and materials will be supplied in Spanish. For participants who are bilingual and prefer procedures implemented in Spanish, all study procedures and materials will be supplied in Spanish.
- Where feasible, self-report, validated measures are sourced from published versions or translated professionally (e.g., Language connections or similar professional service). Bulleted consent forms, advertisements, and other lengthy forms or study materials that would be costly to have professionally translate are translated by a native Spanish speaker who is a member of our research team and reviewed for clarity by a second native Spanish speaker.

23.0 Process to Document Consent in Writing

23.1 Informed consent documentation will adhere to the procedures described in HRP-091-SOP using a bulleted consent form with digital or wet signature from the potential participant witnessed by a trained staff member.

24.0 Setting

24.1 The settings where we will conduct the research include Clínica Esperanza/Hope Clinic (CEHC) at 60 Valley Street in Providence, RI, with the capability to conduct study visits at our primary offices at Brown University SPH 121 S. Main Street in Providence, RI, as well. Our team also has the capacity to reach potential participants through digital and community outreach.

24.2 CEHC was founded in 2007 as a place for patients, volunteers, community partners, and donors to be healthy. CEHC's community health care model ensures that quality care comes from caregivers who are fully integrated in the community. Our partnership between Brown University and CEHC teams will enable us to reach the target underserved population at risk for MetALD.

24.3 CEHC focuses on providing high-quality, culturally attuned, and linguistically appropriate healthcare to all uninsured adults in Rhode Island. CEHC's patient base is primarily made up of Spanish-speaking, Latinx

immigrants from Central and South American countries. CEHC has a core paid staff and a robust network of volunteer medical providers, nurses, medical interpreters, and non-provider volunteers. More than 4,000 patients across nearly 7,000 visits are served annually. CEHC has recently expanded their space, now occupying three suites in the Valley Street location where recruitment will take place.

24.4 CEHC serves a diverse population with significant unmet healthcare needs, including those with alcohol intake and overweight or obesity placing them at increased risk of MetALD. Of CEHC's current patient population, 92% are Latinx, primarily from Central and South America, and 90% are Spanish speaking. Many patients experience immigration-related stress. Many also face instrumental barriers to care, with 4 out of 5 patients living well below the poverty line. More information can be found on CEHC's website, www.aplacetobehealthy.org.

24.5 CEHC is paid through a consultancy for this funded research project. Appropriately compensating clinical partners is best practice for community engagement. CEHC's consultancy fee, approved by their organization, Brown University, and the National Institute of General Medical Sciences, accommodates the use of CEHC resources, including supplies, space, and staff time. Patient navigators, i.e., Navegantes, are trained community health workers assisting with patient care and outreach for CEHC. The assistance of Navegantes with participant recruitment and retention is key to the success of this research. Seamless integration into clinic operations and culturally appropriate approaches are key to successfully reaching underresourced communities.

25.0 Resources Available

25.1 There are ample resources available to conduct the research. Data showing the number and demographics of the patient population served by the CEHC provides evidence for the feasibility of recruiting the designated 40 randomized participants within the timeframe expected. The CEHC serves over 4,000 patients over 7,000 visits annually. Patients commonly have indications of cardiometabolic disease, e.g., hypertension (59%), diabetes (41%), and hyperlipidemia (22%). The CEHC has integrated the AUDIT-C screening tool into their clinical procedures, allowing the research team to identify prospective participants based on BMI and alcohol use. Therefore, this study should meet or exceed the goal of recruiting 1 or 2 participants per week to obtain a final sample of 40 randomized participants in the limited project period. Moreover, the research team is fully prepared to expand recruitment through community or digital outreach and conduct study procedures at our Brown SPH laboratory should it be necessary to meet enrollment targets.

25.2 The research team includes experienced members in multiple roles (e.g., research assistants, project coordinator, medical laboratory technician, faculty investigators, licensed practitioners, interventionists) contributing effort to the project at our partnering sites, in team meetings, in our laboratory, and in related preparations and efforts. The combined effort devoted to this project for the research team triples the project period or more, indicating a very high level of effort committed by the team.

25.3 The research team from Brown will be partnering primarily with the clinical facility described above, the Clínica Esperanza/Hope Clinic (CEHC), which occupies three suites in fully remodeled space in the Olneyville neighborhood in the city of Providence. The CEHC is a highly active clinic providing holistic care including primary medical care, specialty clinics, and related services (e.g., food pantry, community clothing closet) to adults without insurance in Rhode Island. The CEHC has earned the Gold Standard of Care from the National Association of Free and Charitable Clinics and has earned the highest levels of financial transparency awarded to charitable organizations. The Brown SPH facilities occupy three office floors of the 121 S. Main building, where our research team has offices, cubicles, meeting spaces, laboratory space, and usage of the third-floor laboratory preparation room.

25.4 In case of emergency, emergency medical services (EMS) will be called. Participants found to be experiencing medical or physical events that do not require emergency medical services will be evaluated by the study physician or another medical provider at partnering clinical sites or at Brown. An advantage of conducting the study activities at the partnering site is the wealth of clinic and medical staff available to assist in the event of a medical or physical event. In any case, the participant will be encouraged to seek medical care as appropriate.

25.5 In case of an emergency psychiatric event that presents imminent risk of harm to the participant or others, emergency medical services (EMS) will be called. Any participant who is found to be experiencing a psychiatric or psychological issue that is of concern and possible imminent risk will be evaluated by Dr. Treloar Padovano, a licensed clinical psychologist in Rhode Island, or one of several other licensed clinicians on the team.

25.6 The target population at risk for MetALD is also at risk for known or emergent medical issues or events that are not likely to be due to participation in the minimal risk research study. These include but are not limited to events such as hospitalization due to an alcohol-related injury or detoxification from alcohol, hypertension or heart palpitations, or emergencies related to medical events or accidents.

25.7 Processes to ensure that all persons assisting with the research are adequately informed are as follows:

- All team members complete thorough training on the protocol and procedures consistent with their duties on the project. Team members complete CITI training prior to research engagement as well as EHS biosafety training where indicated.
- Weekly team meetings, or more frequent meetings at some stages of training and data collection, ensure that staff are closely supervised and obtain a high level of proficiency.
- Individuals conducting the Fibroscan® are trained operators certified by Echosens, the manufacturer of our Fibroscan® ultrasound machine. Individual Fibroscan® results are reviewed by a study physician who will instruct the team on appropriate next steps and referrals.

- Sessions with the study counselor are audio-recorded with sections selected at random for review and coded by supervisors to ensure fidelity to the intervention protocol. Interventionists are supervised at a minimum biweekly and typically weekly and are given feedback on adherence to the protocol.