Evaluating Signs of Safety: A Deaf-Accessible Therapy Toolkit for AUD and Trauma

This title should include, where possible, information on the participants, condition being evaluated, and intervention(s) studied.

Unique Protocol Identification Number: STUDY00001149

National Clinical Trial (NCT) Identified Number: TBD

Principal Investigator: Melissa L. Anderson

Sponsor:

"Sponsor" indicates an institution, foundation, or individual who takes responsibility for and initiates a clinical investigation; often times this is the university with which the Principal Investigator is affiliated.

Grant Title: Evaluating Signs of Safety: A Deaf-Accessible Therapy Toolkit for AUD and Trauma

Grant Number: R01AA031010

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Version Number: v.1.016

16 February 2024

All versions should have a version number and a date. Use an international date format (e.g.,YYYY-MM-DD [2017-12-21] or write out the month (e.g., 21 December 2017).
For the initial submission of a protocol to the IRB, indicate "Not applicable; this is the first version of the protocol." in the table below. For any subsequent amendment being submitted to the IRB, add details of the specific changes that are being implemented in the amendment. Please note that Section 10.4 is a high-level summary of <u>all</u> formal protocol versions/amendments.

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

Provide a statement that the trial will be conducted in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below. If the study is an ***intramural*** *NIH study, use the second statement below:*

1. The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

    - United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

    National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.
    OR
2. The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the [specify NIH Institute or Center (IC) [Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.
    For either option above, the following paragraph would be included:
    The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

Principal Investigator or Clinical Site Investigator:

Signed:	*Melissa L. Anderson, PhD*	Date:	2/12/2024
Name*:	Melissa L. Anderson, PhD		
Title*:	Associate Professor of Psychiatry and PQHS		

Investigator Contact Information:

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Telephone:	508-856-5820
Email:	melissa.anderson@umassmed.edu

For multi-site studies, the protocol should be signed by the clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site:

Signed:		Date:	
Name:			
Title:			
Affiliation:			

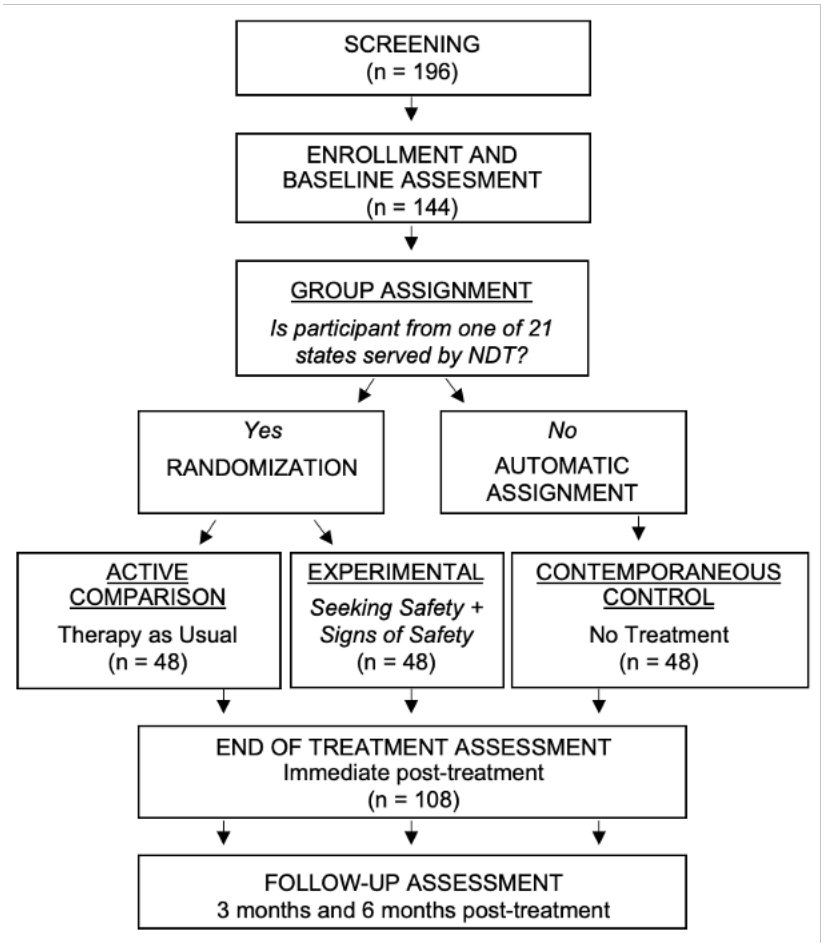
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Evaluating Signs of Safety: A Deaf-Accessible Therapy Toolkit for AUD and Trauma
Grant Number:	R01AA031010
Study Description:	The U.S. Deaf community – a group of more than 500,000 Americans who communicate using American Sign Language (ASL) – experiences nearly triple the rate of lifetime problem drinking and twice the rate of trauma exposure compared to the general population. Although there are several treatments for alcohol use disorder (AUD) and posttraumatic stress disorder (PTSD) in hearing populations, none have been developed for or tested with Deaf clients. To address these barriers, our team developed *Signs* of *Safety*, a Deaf-accessible therapy toolkit for treating AUD and PTSD. We propose a nationwide, virtual clinical trial to compare (1) *Signs* of *Safety* with (2) treatment as usual and (3) a no treatment control, to collect data on clinical outcomes, and to explore potential mediators and moderators of outcome.
Objectives*:	Primary Objective: **Conduct a nationwide, full-scale, virtual clinical trial of *Signs of Safety.*** Leveraging the existing infrastructure and robust referral network of National Deaf Therapy, we will enroll 144 Deaf adults with past-month PTSD and problem drinking into our study protocol. Primary clinical outcomes at immediate post-treatment and post-treatment follow-up are alcohol use frequency/quantity (*Alcohol Timeline Followback*) and PTSD severity (*PTSD Checklist for DSM-5*) since the last assessment timepoint. Assessment will occur at baseline, mid-treatment, immediate post-treatment, three-month post-treatment follow-up, and six-month post-treatment follow-up.
	Secondary Objectives: **Explore potential moderators and mediators that lead to positive outcome**. Identified from the literatures on *Seeking Safety*, alcohol treatment research, and Deaf mental health research, potential mechanisms of change are coping self-efficacy, self-compassion, motivation for treatment, and access to health information.

Endpoints*:	Primary Endpoint:	Alcohol use frequency/quantity (*Alcohol Timeline Followback*) and PTSD severity (*PTSD Checklist for DSM-5*)
	Secondary Endpoints:	DSM-5 Alcohol Use Disorder diagnostic criteria
		Drug use frequency/quantity
		Substance-related problems
		Drug and alcohol craving
		Mental health symptoms
Study Population:	Deaf adults	
Phase* or Stage:	Stage II/III	
Description of Sites/Facilities Enrolling Participants:	National Deaf Therapy (NDT) is a Deaf-female-owned agency that is by far the nation's largest provider of Deaf mental health services. NDT specializes in personalized telemental health care for Deaf individuals. NDT reaches 400+ persons served annually across 24 U.S. states.	
Description of Study Intervention/Experimental Manipulation:	*Signs of Safety* is a Deaf-accessible toolkit to be used with the *Seeking Safety* treatment protocol. *Seeking Safety* is a manualized, non-exposure-based, cognitive behavioral therapy for trauma and addiction. Experimental participants will be offered 12 one-hour, weekly individual therapy sessions of *Seeking Safety* delivered with the *Signs of Safety* toolkit. Sessions will occur virtually via NDT's secure HIPAA-compliant video chat platform. The length of treatment is limited to six months; the number of completed sessions will be tracked as a measure of participant adherence.	
Study Duration*:	48 months	
Participant Duration:	9 months to 1 year	

1.2 SCHEMA


SCREENING
(n = 196)
ENROLLMENT AND
BASELINE ASSESMENT
(n = 144)
GROUP ASSIGNMENT
Is participant from one of 21 states served by NDT?
Yes
RANDOMIZATION
No
AUTOMATIC ASSIGNMENT
ACTIVE COMPARISON
Therapy as Usual
(n = 48)
EXPERIMENTAL
Seeking Safety + Signs of Safety
(n = 48)
CONTEMPORANEOUS CONTROL
No Treatment
(n = 48)
END OF TREATMENT ASSESSMENT
Immediate post-treatment
(n = 108)
FOLLOW-UP ASSESSMENT
3 months and 6 months post-treatment

1.3 SCHEDULE OF ACTIVITIES

Table 2: Study Enrollment Flow Chart
(e = # of participants enrolled in the study thus far; ✓ = # of participants who have completed the study protocol)

R01 YEAR 2											
1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
e = 4 ✓= 0	e = 8 ✓= 0	e = 12 ✓= 0	e = 16 ✓= 0	e = 20 ✓= 0	e = 24 ✓= 0	e = 28 ✓= 0	e = 32 ✓= 0	e = 36 ✓= 0	e = 40 ✓= 0	e = 44 ✓= 0	e = 48 ✓= 0
R01 YEAR 3											
13	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*
e = 52 ✓= 4	e = 56 ✓= 8	e = 60 ✓= 12	e = 64 ✓= 16	e = 68 ✓= 20	e = 72 ✓= 24	e = 76 ✓= 28	e = 80 ✓= 32	e = 84 ✓= 36	e = 88 ✓= 40	e = 92 ✓= 44	e = 96 ✓= 48
R01 YEAR 4											
25	*26*	*27*	*28*	*29*	*30*	*31*	*32*	*33*	*34*	*35*	*36*
e = 100 ✓= 52	e = 104 ✓= 56	e = 108 ✓= 60	e = 112 ✓= 64	e = 116 ✓= 68	e = 120 ✓= 72	e = 124 ✓= 76	e = 128 ✓= 80	e = 132 ✓= 84	e = 136 ✓= 88	e = 140 ✓= 92	e = 144 ✓= 96
R01 YEAR 5											
37	*38*	*39*	*40*	*41*	*42*	*43*	*44*	*45*	*46*	*47*	*48*
e = 144 ✓=100	e = 144 ✓= 104	e = 144 ✓=108	e = 144 ✓=112	e = 144 ✓=116	e = 144 ✓=120	e = 144 ✓=124	e = 144 ✓= 128	e = 144 ✓= 132	e = 144 ✓= 136	e = 144 ✓= 140	e = 144 ✓= 144

Table 3: Clinical Outcome Measures

Domain	Measure (**bold** = *primary outcome*)	# of items
Alcohol and Drug Use	*AUD Identification Test*	10
	Alcohol Timeline Followback	4
	DSM-5 AUD Assessment Tool	13
	Timeline Followback – Drugs, Cigarettes, and Marijuana	5
	Short Inventory of Problems Revised	17
	Alcohol and drug craving items from the Brief Addiction Monitor – Revised	2
PTSD and Psychosocial Functioning	***PTSD Checklist for DSM-5***	20
	Outcome Questionnaire (OQ-30.2) for Adults	30
Mediators and Moderators of Change	*Contemplation Ladder*	1
	Brief Resilient Coping Scale	4
	Self-Compassion Scale – Short Form	12
	Ask, Understand, Remember Assessment	4
Satisfaction	*Satisfaction with Therapy & Therapist Scale*	12

2 INTRODUCTION

2.1 STUDY RATIONALE

In partnership with Deaf-owned agency National Deaf Therapy, we will conduct the first-ever full-scale psychotherapy trial conducted in the Deaf community - "**Evaluating *Signs of Safety:* A Deaf-Accessible Therapy Toolkit for AUD and Trauma.**" The U.S. Deaf community – more than 500,000 Americans who communicate using American Sign Language (ASL)[2] – experiences nearly triple the rate of lifetime problem drinking compared to the general population (33.0% vs. 12.3%)[3,4,5,6] and twice the rate of trauma exposure.[7,8,9,10,11] Among Deaf people in treatment for alcohol use disorder (AUD), 74% report lifetime physical, emotional, or sexual abuse and 44% report past-year abuse.[4] Comorbid AUD/PTSD impairs multiple domains of functioning,[12] especially for Deaf individuals, who show poorer functional outcomes than hearing individuals in socialization,[13] employment,[13] and physical health.[14]
Hearing individuals have access to several validated treatments for comorbid AUD/PTSD;[15,16,17,18,19] yet there are **no evidence-based treatments** to treat **any behavioral health condition** with Deaf clients.[20,21] Available treatments fail to meet Deaf clients' unique language access needs.[20] Deaf people's median English literacy level falls at the fourth grade[22] and health-related vocabulary among Deaf sign language users parallels non-English-speaking U.S. immigrants.[23] Available treatment resources, therefore, require plain text revisions, filmed ASL translations, or education through storytelling to better match Deaf clients' language needs.[24,25,26]
Leveraging extensive community engagement to address these barriers, the PI's team of Deaf and hearing researchers, clinicians, filmmakers, actors, artists, and Deaf people with AUD/PTSD developed and pilot tested ***Signs of Safety****,* a Deaf-accessible toolkit to be used with the *Seeking Safety* treatment protocol.[19] *Seeking Safety* is a manualized, non-exposure-based, cognitive behavioral therapy for trauma and addiction. Among evidence-based treatments for AUD/PTSD, *Seeking Safety* is the optimal choice for Deaf clients – its focus on **psychoeducation** and **simple coping skills** is an **ideal match for Deaf people's language and literacy disparities**, which prohibit the use of narrative, verbal problem-solving, and cognitive processing strategies that other AUD/PTSD therapies require.[27] Yet, *Seeking Safety*'s client materials rely on written English and are, therefore, not well understood by Deaf clients. As such, the *Signs of Safety* toolkit provides a supplemental therapist guide and population-specific client materials (e.g., visual handouts, filmed ASL teaching stories).
Preliminary data from the *Signs of Safety* single-arm pilot and randomized feasibility pilot showed **reductions in alcohol use frequency and PTSD severity** from baseline to follow-up on the Reliable Change Index.[28] The delivery of the experimental intervention was deemed feasible by study therapists and was well-received by participants,[28] especially when moved to a virtual platform. In response to the COVID-19 pandemic, we overhauled in-person study methods to implement a virtual clinical trial – an **acceleration of the inevitable development needed to scale *Signs of Safety* to a national level**. This adaptation also established a crucial collaboration with National Deaf Therapy (NDT), by far the nation's largest provider of Deaf mental health services, currently serving clients across 21 states. This collaboration, paired with comprehensive feasibility data we collected by testing a variety of virtual methods, serves as the foundation of our proposed aims:

Aim 1: Conduct a nationwide, full-scale, virtual clinical trial of *Signs of Safety.* Leveraging the existing infrastructure and robust referral network of NDT, we will enroll 144 Deaf adults with past-month PTSD and problem drinking into our study protocol. Primary clinical outcomes at immediate post-treatment and post-treatment follow-up are past 30-day alcohol use frequency/quantity (*Alcohol Timeline Followback*)[29] and past 30-day PTSD severity (*PTSD Checklist for DSM-5*).[30] Assessment will occur at baseline, mid-treatment, immediate post-treatment, three-month post-treatment follow-up, and six-month post-treatment follow-up.

Aim 1a: Participants residing in the 21 states served by NDT (n = 96) will be randomized to receive either (1) a 12-session protocol of *Seeking Safety* + *Signs of Safety,* or (2) 12 sessions of therapy as usual (TAU; general, open-ended, non-manualized supportive counseling provided by an NDT therapist).

Aim 1b: Augmenting the Aim 1a RCT, we will enroll an additional 48 Deaf adults into a contemporaneous no-treatment control arm. These individuals will be recruited from the existing NDT waitlist, comprised of Deaf individuals residing in the 29 states not yet served by NDT but voluntarily awaiting NDT services.

Aim 2: Analyze potential moderators and mediators that lead to positive outcome. Identified from the literatures on *Seeking Safety*, alcohol treatment research, and Deaf mental health research, mechanisms of change are coping self-efficacy, self-compassion, motivation for treatment, and access to health information.

Our proposed aims build on eight years of KL2 and R34 empirical work, moving this program of research from Stage IB (two-arm feasibility and pilot testing) to Stage II/III (real world efficacy). The proposed R01 will potentially validate the first-ever evidence-based therapy for Deaf people, as well as provide future behavioral health researchers with a vital roadmap for conducting community-engaged clinical trials with Deaf people.

2.2 BACKGROUND

SIGNIFICANCE

A1. Deaf people experience triple the rate of lifetime problem drinking and double the rate of trauma exposure compared to the general population.[3,4,5,6,7,8,9,10,11] The U.S. Deaf community – a group of 500,000+ Americans who communicate using American Sign Language (ASL)[2] – reports nearly three times the rate of lifetime problem drinking compared to the general population (33.0% vs. 12.3%; adjusted OR = 2.5, p = 0.0004).[3] An estimated 15% of Deaf Americans meet criteria for current alcohol use disorder (AUD),[31] with high rates of comorbid posttraumatic stress disorder (PTSD) complicating their recovery.[12] Deaf individuals report double the rate of interpersonal trauma compared to hearing peers,[7,8,9,10,11] with the PI's research finding that 61% of Deaf college women experienced past-year sexual coercion (hearing = 28%) and 52% past-year physical assault (hearing = 28%).[7,32] Among Deaf people in AUD treatment, 74% report lifetime physical, emotional, or sexual abuse and 44% report past-year abuse.[4]

Comorbid AUD/PTSD complicates treatment and affects multiple domains of functioning.[12] Hearing individuals with this comorbidity have greater physical and social impairment, higher rates of mood, anxiety, and personality disorders, and increased trauma-related craving (i.e., craving substances in response to PTSD symptoms) compared to those with AUD alone.[17,33,34] Deaf people show even greater impairment than hearing peers, with poorer outcomes in socialization,[13] employment,[13] and physical health.[14] These pervasive disparities stress the critical need for accessible, validated AUD/PTSD treatments for Deaf clients.

A2. Although hearing clients have access to several validated treatments for comorbid AUD/PTSD, there are *no* evidence-based treatments for *any* behavioral health condition that have been developed for or formally evaluated with Deaf clients.[20,21,28] Currently available treatments fail to meet the unique language needs of Deaf clients.[20] Deaf people's median reading level falls at the fourth grade.[22] Health-related vocabulary parallels non-English-speaking U.S. immigrants.[23] Many have minimal understanding of basic recovery concepts (e.g., *substance, relapse, trigger)*[35] and are unaware that being hit, choked, or coerced into sex is considered *abuse*.[32] Such health literacy gaps are caused by a lifetime of impoverished communication access to health education materials, healthcare professionals, and one's own parents.[36,37] Written treatment materials, therefore, require plain text revisions, ASL translations, or education through storytelling.[24,25,26]

Moreover, due to lack of early language exposure, poor educational experiences, and resulting long-term language dysfluency, many Deaf adults enter treatment unable to construct a narrative or a coherent timeline of events.[24,38] Therefore, the narrative, verbal problem-solving, and cognitive processing strategies required by most evidence-based AUD/PTSD therapies are contraindicated in the treatment of many Deaf clients.[27]

A3. Leveraging extensive community engagement to address these barriers, our team created *Signs of Safety,*[28] a Deaf-accessible therapy toolkit to be used with an existing treatment for trauma and addiction – *Seeking Safety.*[19] *Seeking Safety* is a manualized, non-exposure-based, cognitive behavioral therapy that focuses on psychoeducation and development of simple coping skills that simultaneously target AUD and PTSD (or either alone). *Seeking Safety* is the most widely implemented model for PTSD and substance use disorder, with a 2016 meta-analysis indicating positive outcomes on both PTSD and substance use disorder among 1000+ patients across studies.[1,39,40,41,42,43,44] Although there is preliminary-to-promising evidence for other manualized treatments for comorbid AUD/PTSD,[16,18,33,45] these treatments rely on the client's ability to formulate a trauma narrative,[55] which, as described above in section A2, is contraindicated for many Deaf clients.[7,35] Such models also have limitations for Deaf clients from a public health standpoint (e.g., more costly, exclude more complex clients).[56]

Given these contraindications, our team selected *Seeking Safety* as our base intervention due to its present-focus (i.e., no need to retell the trauma narrative) and reliance on simple coping skills. Notably, among women with disabilities,[57] those treated with *Seeking Safety* experienced sustained reductions in PTSD symptoms while women in the comparison condition experienced experienced full PTSD recurrence by 12-month follow-up.[57] Changes in AUD over time could not be investigated in this secondary analysis, as the majority of participants with disabilities reported no alcohol use at baseline. Despite this floor effect, this study provided preliminary support that *Seeking Safety* would be an engaging and effective approach among individuals with disabilities, including Deaf individuals.[57] Indeed, *Seeking Safety* has been used successfully with highly diverse populations, translated into 14 foreign

languages, and aligns with most strategies for Deaf-friendly treatment – skill-building and psychoeducation, structured sessions, case management, present focus, and strength-based work.[27,58] Yet, similar to other manualized treatments, *Seeking Safety* 's client materials rely on written English, failing to meet the linguistic needs of Deaf clients.[20,35]

To address this barrier, the PI assembled an impressive team of Deaf and hearing researchers, clinicians, filmmakers, actors, artists, and Deaf people with AUD/PTSD to develop and pilot test *Signs of Safety,* a Deaf-accessible toolkit to be used with *Seeking Safety*. A similar toolkit approach has been used to augment *Seeking Safety* for adolescents[59] and individuals with HIV.[60] To develop *Signs of Safety,* our team followed NIDA behavioral therapy development approaches[61] and recommended principles for creating Deaf-accessible interventions: language adaptations and simplification of English-based materials; use of teaching stories and examples; inclusion of visual aids; active treatment strategies and role-playing; attention to health literacy gaps; leveraging of technology; and, drawing on Deaf community members' desire to help and teach each other.[27,58] For future generalizability and public health impact, *Signs of Safety* is designed for use by both Deaf/signing clinicians and non-signing clinicians who communicate with Deaf clients through ASL interpreters.

Signs of Safety includes two primary components:

The **therapist companion guide** teaches clinicians how to effectively implement *Seeking Safety* with Deaf clients by providing recommended ASL translations of common *Seeking Safety* concepts and vocabulary, exploring how issues raised by each *Seeking Safety* topic interact with common Deaf experiences, and discussing helpful tips for working with Deaf clients with addiction and PTSD.

Client materials include: (1) ASL teaching stories on digital video for 12 core *Seeking Safety* topics, which present critical learning points portrayed by Deaf actors; and (2) visual handouts, which present key information using plain text and visual aids created by a Deaf artist.

To design the main component of *Signs of Safety* – the ASL teaching stories described above – we leveraged the cultural tradition of storytelling in the Deaf community.[62] Additionally, we drew on the Slater Model of Narrative Communication,[25,26] in which a compelling storyline, the level of similarity between the characters and the audience, and high production quality coalesce to produce changes in attitudes, skills, and behaviors.

To formally test the efficacy of *Signs of Safety*, we will partner with National Deaf Therapy to conduct a nationwide, full-scale virtual clinical trial. The proposed R01 builds on eight years of KL2 and R34 research, moving this program from Stage IB (two-arm feasibility and pilot testing) to Stage II/III (real world efficacy).

INNOVATION

This program of research is infused with innovation, from study start-up through end-of-study dissemination:

- We will conduct the **first-ever** full-scale psychotherapy clinical trial in the Deaf community.
- We will formally translate validated, commonly used, open access behavioral health measures from written English to ASL. **None of our proposed measures are currently available in ASL** in the public domain; we will make the resulting ASL translations publicly available for behavioral health researchers and clinicians who work with Deaf people to further increase the public health impact of our research.

- We will apply an exceptional level of community engagement throughout the research process:
    - The team is co-led by a **Deaf co-investigator**, a significant feat given that only 1% of science and engineering doctorates are earned by Deaf or hard-of-hearing individuals.[63]
    - We will hire **four Deaf Community Advisors** onto the team – Deaf laypeople with lived experience of AUD and/or PTSD who will help guide online survey development, study methods and recruitment, interpretation of findings, and dissemination back to the Deaf community.

We are partnering with **National Deaf Therapy**, a Deaf-female-owned company that specializes in personalized tele mental health care for Deaf individuals. Given the agency's reach of 400+ persons served annually across 21 U.S. states, this partnership will also serve as an essential mechanism for end-of-study dissemination of *Signs of Safety* into the larger Deaf community.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There is a potential risk of loss of confidentiality. There is a potential risk of discomfort or increased mental health symptoms associated with completing study interventions and assessments. There is also a potential risk of experiencing alcohol withdrawal symptoms. We address each below:

Risks associated with potential loss of confidentiality. There is a slight risk that research records (e.g., assessment data, video recordings) might be obtained by unauthorized persons. There is a slight risk that research data files might be compromised and obtained or viewed by unauthorized persons.

Risks associated with study interventions and assessments. Potential risks to participants include an increase in mental health symptoms while participating in *Seeking Safety/Signs of Safety* therapy, a known risk of participating in treatment in general. Additionally, completing study-related assessments may cause potential risk to participants, including discomfort, embarrassment, triggers of PTSD symptoms, or triggers of substance cravings.

Risks associated with reductions in alcohol use. Another potential risk to participants with severe AUD is symptoms of alcohol withdrawal.

2.3.2 KNOWN POTENTIAL BENEFITS

The following potential benefits cannot be guaranteed. Potential benefits to participants include:

• Access to an evidence-based intervention (Seeking Safety) and treatment materials that they may not otherwise be able to access.

• Decrease in mental health symptoms and addiction severity.

• Increase in safe coping skills and ability to manage their trauma symptoms.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Risks associated with potential loss of confidentiality. Comprehensive procedures to protect participants' confidentiality are described in **Section 10.1.3 - Confidentiality and Privacy.**

Risks associated with study interventions and assessments. Potential risks to participants include an increase in mental health symptoms while participating in *Seeking Safety/Signs of Safety* therapy, a known risk of participating in treatment in general, but not a pattern that has previously been identified with *Seeking Safety* or in the *Signs of Safety* preliminary studies. Rather, participants in *Seeking Safety* are instructed not to delve deeply into trauma details, with the purpose of minimizing exposure and adverse responses to trauma triggers. Additionally, completing study-related assessments may cause potential risk to participants, including discomfort, embarrassment, triggers of PTSD symptoms, or triggers of substance cravings. Our procedures for protecting against and managing such risks are described in the attached "NIAAA Data and Safety Monitoring Plan."

Risks associated with reductions in alcohol use. Another potential risk to participants with severe AUD is symptoms of alcohol withdrawal. Study therapists will be trained to have a low threshold for alcohol withdrawal risk. For any participants reporting alcohol discontinuation, study therapists will ask participants if they are experiencing any significant symptoms of withdrawal - tremors, sweating, flushing, nausea, vomiting, hallucinations, or seizures. If a participant endorses any of these symptoms, the therapist will briefly pause the session to consult with Co-I Jefee-Bahloul, Addiction Psychiatrist, who will be available for on-call phone consultation. Given the potential lethality of alcohol withdrawal, Dr. Jefee-Bahloul will likely recommend voluntarily sending the participant to detox or the Emergency Department for evaluation (Note: Prior to study initiation, our team will work with National Deaf Therapy to identify detox programs in each state where study intervention will be provided). Following the therapy session, the therapist will report the event to PI Anderson.

Any serious adverse events, unanticipated problems, or breaches of confidentiality that occur during the intervention period and/or the one-month follow-up period will be reported to the UMass Chan Institutional Review Board and the NIAAA project officer within 48 hours. Additionally, an annual report will be submitted to the NIAAA project officer summarizing all adverse events.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
Conduct a nationwide, full-scale, virtual clinical trial of *Signs of Safety.* Leveraging the existing infrastructure and robust referral network of National Deaf Therapy, we will enroll 144 Deaf adults with past-month PTSD and problem drinking into our study protocol. Primary clinical outcomes at immediate post-treatment and post-treatment follow-up are alcohol use frequency/quantity (*Alcohol Timeline Followback*) and PTSD severity (*PTSD Checklist for DSM-5*) to the last assessment timepoint. Assessments will occur at baseline, mid-treatment, immediate post-treatment, three-month post-treatment follow-up, and six-month post-treatment follow-up.	Alcohol use frequency/quantity (*Alcohol Timeline Followback*); PTSD severity (*PTSD Checklist for DSM-5*)	Measures of primary clinical outcome are: the *Alcohol Timeline Followback,*[28] to assess daily drinking frequency and quantity for a selected time range (we will use "past 30 days" at baseline and "time since to assessment" for all other timepoints); and the *PTSD Checklist for DSM-5,*[29] a measure of DSM-5 PTSD symptoms that is reliably used to monitor symptom change.[70]	TBD: See Tertiary/Exploratory Below.
Secondary			

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Same as above.	DSM-5 Alcohol Use Disorder diagnostic criteria; Drug use frequency/quantity; Substance-related problems; Drug and alcohol craving; Mental health symptoms.	Measures of secondary clinical outcome are the *Timeline Followback – Drugs, Cigarettes, and Marijuana,* which we will use to assess frequency and quantity of drug use for the same referent time period; the *DSM-5 AUD Assessment Tool* to track AUD symptoms over time; the *Short Inventory of Problems Revised,* to assess alcohol-related consequences; two items querying alcohol and drug craving from the *Brief Addiction Monitor – Revised*; and the *Outcome Questionnaire (OQ-30.2) for Adults*, to assess changes in psychosocial functioning over time.	TBD: See Tertiary/Exploratory Below.
Tertiary/Exploratory			
Explore potential moderators and mediators that lead to positive outcome. Identified from the literatures on *Seeking Safety*, alcohol treatment research, and Deaf mental health research, potential mechanisms of change are coping self-efficacy, self-compassion, motivation for treatment, and access to health information.	Coping self-efficacy; Self-compassion; Motivation for treatment; access to health information.	We identified potential mechanisms of change from the *Seeking Safety* literature, alcohol treatment literature, and Deaf mental health literature. One key moderator is motivation for treatment.[74,75,76] Potential mediators are participants' reported ability to use coping skills,[39,72,77,78] practice self-compassion,[72,79,80,81] and understand health information.[23,34,35,36,58] These constructs will be measured by the *Contemplation Ladder,*[82,83] a single-choice, visual analogue scale whose higher rungs represent greater levels of readiness to	N/A

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
		change; the *Brief Resilient Coping Scale,*[84,85] a measure of perceived ability to effectively use coping strategies in flexible, committed ways to actively solve problems despite stressful circumstances; the *Self-Compassion Scale – Short Form,*[86] a measure of self-compassion in instances of perceived failure, inadequacy, or suffering; and, the *Ask, Understand, Remember Assessment (AURA),*[87] a measure of one's ability to obtain, understand, and remember health information communicated by a provider.	

4 STUDY DESIGN

4.1 OVERALL DESIGN

In partnership with National Deaf Therapy (NDT) and informed by feasibility data generated during the *Signs of Safety* single-arm pilot and randomized feasibility pilot (see preliminary data in section 4.2), we will conduct a nationwide, full-scale, virtual clinical trial of *Signs of Safety.* To prepare, we will fine-tune our therapist training program and certify eight study therapists from NDT in *Seeking Safety* + *Signs of Safety.* Additionally, to streamline study outcome assessment, we will formally translate study measures from written English to ASL, professionally film the final translations, and design a Deaf-accessible online REDCap survey platform.

Across three years of rolling recruitment, we will recruit 144 Deaf adults with past-month PTSD and problem drinking into our study protocol (**Aim 1**). Primary clinical outcomes at immediate post-treatment and follow-up are alcohol use frequency/quantity (*Alcohol Timeline Followback*)[29] and PTSD severity (*PTSD Checklist for DSM-5*)[30] since the last assessment timepoint. Assessments will occur at baseline, mid-treatment (week 6), immediate post-treatment (week 12), three-month post-treatment follow-up, and six-month post-treatment follow-up.

Participants residing in the 21 states served by NDT (n = 96) will be randomized to receive either (1) a 12-session protocol of *Seeking Safety* + *Signs of Safety,* or (2) 12 sessions of therapy as usual (**Aim 1a**). Augmenting the Aim 1a RCT, we will enroll an additional 48 Deaf adults into a contemporaneous no-treatment control arm. These individuals will be recruited from the existing NDT waitlist, comprised of Deaf individuals residing in the 29 states not yet served by NDT but voluntarily awaiting NDT services (**Aim 1b**).

We will also explore potential moderators and mediators that may lead to positive outcomes, including participants' coping self-efficacy, self-compassion, motivation for treatment, and perceived access to health information (**Aim 2**).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This *Signs of Safety* clinical trial is informed by two foundational studies – a single-arm open pilot study (2014 – 2019) and a pilot feasibility randomized controlled trial (2018 – 2022).

Open Pilot Study (2014 – 2019)

PI Anderson's single-arm open pilot study resulted in the successful creation of the *Signs of Safety* toolkit prototype, the demonstration of recruitment feasibility and acceptability of the study intervention, and evidence of preliminary efficacy. Participants (*n* = 13) reported high levels of satisfaction with the *Seeking Safety* + *Signs of Safety* intervention. This finding was supported by a 23% attrition rate (3/13), lower than the average rate of 27% observed in longitudinal addiction studies.[64] Our attrition rate was especially noteworthy given that retained participants completed a lengthy 25-session treatment protocol and end-of-treatment assessment.

Clinically meaningful reductions in alcohol use frequency and PTSD severity were observed from baseline to immediate post-treatment.[28] Participants who received the minimum dose of *Seeking Safety* + *Signs of Safety* (at least six sessions; *n* = 10) exhibited a 9.9 point mean reduction on the *PTSD Checklist for DSM-5* (*PCL-5*),[28] aligning with the 10 point clinically meaningful improvement on this measure.[65] Alcohol use frequency decreased by an average of 4.7 days per month across the course of the study. Eight participants (80.0%) were abstinent or evidenced clinically meaningful reduction in past-month alcohol use by the end of treatment (Reliable Change Index > 1.96), one remained unchanged, and one increased their drinking.[28]

Randomized Feasibility Pilot (2018 – 2022)

The *Signs of Safety* randomized feasibility pilot resulted in the professional production of a final version of the *Signs of Safety* toolkit*,* the development and successful implementation of a prototype therapist training program, and the mid-2019 launch of an in-person, two-arm pilot feasibility randomized controlled trial. Just as enrollment ramped up, our trial was disrupted by the onset of the COVID-19 pandemic. In response, we paused the study to overhaul our in-person research methods and instead implement a virtual clinical trial – an acceleration of the inevitable development needed to scale *Signs of Safety* to a national level. This adaptation made possible our crucial collaboration with National Deaf Therapy, as well as provided comprehensive feasibility data from testing a variety of virtual clinical trial methods. These data informed our proposed methods and are interspersed throughout the Approach in sections labeled ***Feasibility Findings***.

Despite significant COVID-related disruptions, the delivery of the experimental intervention was deemed feasible by study therapists and was well-received by participants,[28] especially after we moved to a virtual platform. Initial outcome data reinforce the preliminary efficacy observed during the *Signs of Safety* open pilot. Using intent-to-treat analyses, participants assigned to the active treatment arm (*n* = 8) exhibited a 22% decrease in PTSD symptom severity from baseline to follow-up, compared to a 9% decrease among those assigned to waitlist control (*n* = 7). Active treatment participants exhibited an 8-point mean reduction on the *PCL-5,* especially notable considering the intervention protocol reduced from 25 treatment sessions in the open pilot to 12 sessions in the pilot feasibility RCT. Active treatment participants reduced binge drinking by 1.75 days per month, as compared to 0.14 days per month in the waitlist control arm. Two participants in active treatment became fully abstinent from alcohol by follow-up, as compared to none of the waitlist participants.

4.3 JUSTIFICATION FOR INTERVENTION

Seeking Safety is a manualized, non-exposure-based, cognitive behavioral therapy that focuses on psychoeducation and development of simple coping skills that simultaneously target AUD and PTSD (or either alone). *Seeking Safety* is the most widely implemented model for PTSD and substance use disorder, with a 2016 meta-analysis indicating positive outcomes on both PTSD and substance use disorder among 1000+ patients across studies.[1,39,40,41,42,43,44] Although there is preliminary-to-promising evidence for other manualized treatments for comorbid AUD/PTSD,[16,18,33,45] these treatments rely on the

client's ability to formulate a trauma narrative,[55] which, as described above in section 2.1, is contraindicated for many Deaf clients.[7,35] Such models also have limitations for Deaf clients from a public health standpoint (e.g., more costly, exclude more complex clients).[56]

Given these contraindications, our team selected *Seeking Safety* as our base intervention due to its present-focus (i.e., no need to retell the trauma narrative) and reliance on simple coping skills. Notably, among women with disabilities,[57] those treated with *Seeking Safety* experienced sustained reductions in PTSD symptoms while women in the comparison condition experienced experienced full PTSD recurrence by 12-month follow-up.[57] Changes in AUD over time could not be investigated in this secondary analysis, as the majority of participants with disabilities reported no alcohol use at baseline. Despite this floor effect, this study provided preliminary support that *Seeking Safety* would be an engaging and effective approach among individuals with disabilities, including Deaf individuals.[57] Indeed, *Seeking Safety* has been used successfully with highly diverse populations, translated into 14 foreign languages, and aligns with most strategies for Deaf-friendly treatment – skill-building and psychoeducation, structured sessions, case management, present focus, and strength-based work.[27,58] Yet, similar to other manualized treatments, *Seeking Safety* 's client materials rely on written English, failing to meet the linguistic needs of Deaf clients.[20,35]

To address this barrier, the PI assembled an impressive team of Deaf and hearing researchers, clinicians, filmmakers, actors, artists, and Deaf people with AUD/PTSD to develop and pilot test *Signs of Safety,* a Deaf-accessible toolkit to be used with *Seeking Safety*. A similar toolkit approach has been used to augment *Seeking Safety* for adolescents[59] and individuals with HIV.[60] To develop *Signs of Safety,* our team followed NIDA behavioral therapy development approaches[61] and recommended principles for creating Deaf-accessible interventions: language adaptations and simplification of English-based materials; use of teaching stories and examples; inclusion of visual aids; active treatment strategies and role-playing; attention to health literacy gaps; leveraging of technology; and, drawing on Deaf community members' desire to help and teach each other.[27,58] For future generalizability and public health impact, *Signs of Safety* is designed for use by both Deaf/signing clinicians and non-signing clinicians who communicate with Deaf clients through ASL interpreters.

Signs of Safety includes two primary components:

The **therapist companion guide** teaches clinicians how to effectively implement *Seeking Safety* with Deaf clients by providing recommended ASL translations of common *Seeking Safety* concepts and vocabulary, exploring how issues raised by each *Seeking Safety* topic interact with common Deaf experiences, and discussing helpful tips for working with Deaf clients with addiction and PTSD.

Client materials include: (1) ASL teaching stories on digital video for 12 core *Seeking Safety* topics, which present critical learning points portrayed by Deaf actors; and (2) visual handouts, which present key information using plain text and visual aids created by a Deaf artist.

To design the main component of *Signs of Safety* – the ASL teaching stories described above – we leveraged the cultural tradition of storytelling in the Deaf community.[62] Additionally, we drew on the Slater Model of Narrative Communication,[25,26] in which a compelling storyline, the level of similarity between the characters and the audience, and high production quality coalesce to produce changes in attitudes, skills, and behaviors.

4.4 END-OF-STUDY DEFINITION

An active treatment participant is considered to have completed the study if they have completed all 12 intervention sessions, as well as all assessment time points (baseline, mid-treatment/week 6, immediate post-treatment/week 12, three-month post-treatment follow-up/week 25, and six-month post-treatment follow-up/week 38.)

A no-treatment control participant is considered to have completed the study if they have completed all assessment time points (baseline, mid-treatment/week 6, immediate post-treatment/week 12, three-month post-treatment follow-up/week 25, and six-month post-treatment follow-up/week 38.)

The end of the study is defined as completion of the 6-month follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

• Self-identification as Deaf or hard-of-hearing
• Proficiency in American Sign Language (ASL)
• Age 18 years or older
• Access to videoconferencing technology for informed consent and, if applicable, study therapy sessions
• Access to online survey technology for study assessments
• "Problematic alcohol consumption, drinking behaviors, and alcohol-related problems" on the AUD Identification Test (AUDIT),[71] a 10-item screening measure developed by the World Health Organization that demonstrates good sensitivity and specificity in many populations[72,73,74] (past-month referent time period; score ≥ 8 for men or ≥ 6 for women)
• "Subthreshold or full PTSD," on the PTSD Checklist for DSM-5 (PCL-5),[30] a 20-item measure of PTSD symptoms reliably used to monitor symptom change[75] (past-month referent time period; "subthreshold" = meets at least two DSM-5 diagnostic categories (B, C, D, and/or E) at moderate or high severity[76])

Baseline AUDIT scores of 8 to 19 are appropriate for brief research interventions[77] such as our 12-session protocol, and subthreshold PTSD is associated with levels of impairment comparable to full PTSD (i.e., social/work functioning, suicide attempts).[78] Moreover, we intentionally include individuals across the full range of severity of both AUD and PTSD for the broadest possible public health relevance.[79]

5.2 EXCLUSION CRITERIA

• Participation in concurrent formal psychotherapy (Note: Participants in all study conditions will be asked to refrain from concurrent formal psychotherapy. Participants who engage in formal psychotherapy outside of the research will be removed from the study at the point of treatment initiation. Outside treatment engagement will be queried at each assessment timepoint. If endorsed, the participant will be removed from the study at that timepoint, but data collected prior to treatment initiation will remain in the dataset. Aligning with the Seeking Safety model, AA/NA/DRA attendance will be encouraged; attendance will be tracked as a potential outcome mediator.)
• Members of the following special populations: Adults unable to consent; Individuals younger than 18 years; Prisoners; Pregnant women (Note: We will not knowingly include pregnant women as participants; however, we will not assess participants' pregnancy status.)

Exclusion criteria are intentionally minimal to recruit a diverse sample. Other behavioral health comorbidities (e.g., mood/anxiety disorders, substance use disorders other than AUD) will not be excluded, given high rates of comorbidity.[72]

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include increases in alcohol use or PTSD symptoms that would then meet the threshold for study participation. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Study recruitment will leverage the existing infrastructure and robust referral network of National Deaf Therapy (NDT). NDT receives more than 600 new client referrals per year; this projects to approximately 1,800 referrals across the course of our three-year rolling recruitment phase. During open recruitment, new clients who present to NDT to address issues of trauma and/or alcohol use will be asked if they are potentially interested in participating in the *Signs of Safety* clinical trial. Interested individuals will be sent a link to our eligibility screening survey via email or text. Those who are eligible will be promptly contacted by our research team for informed consent procedures, described in more detail in section 10.1.

Our research team will further support study advertisement by disseminating ASL recruitment videos and plain English flyers to Deaf-related organizations, Facebook groups, and listservs across the US. The PI has used such methods successfully in six previous studies involving Deaf research participants.[6,31,93,94,95] Recruitment materials will direct interested individuals to contact NDT for eligibility screening.

To evaluate feasibility of recruitment, we analyzed one year of NDT's diagnostic billing data (5/1/2021 – 4/30/2022). In this period, 21.8% of clients presented with PTSD or a trauma-related disorder; NDT therapists estimate that approximately half of those with PTSD also reported alcohol-related problems

(10.9% of NDT clientele). Projected onto 1,800 new referrals during our rolling recruitment period, we anticipate that approximately 196 individuals will meet study eligibility criteria across our three-year recruitment period. In the *Signs of Safety* randomized feasibility pilot, 83% of eligible individuals chose to enroll in the study protocol. Applying a more conservative enrollment rate of 75% to the proposed trial, we estimate that, of the 196 projected positive eligibility screens, at least 144 individuals will enroll.

To evaluate anticipated sample diversity**,** we analyzed deidentified demographic data for the 10.9% of NDT clientele who would likely meet eligibility criteria for the proposed study. Assuming stable demographic characteristics over time, data suggests a median participant age of 34 years (range = 26 to 66 years). Approximately 63% of the sample will be non-Hispanic White, 20% Hispanic/Latino, 3% Black/African American, and 14% other race/ethnicity. Approximately 77% of the sample will be female, 10% male, and 13% other gender identity (e.g., non-binary, transgender).

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Assignment to condition. After baseline assessment is complete, study staff will assign participants to study condition. The PI and all Co-Is will be masked to study condition. Assignment will adhere to **ethical and legal obligations** to match participants with **therapists licensed to practice in the participant's state of residence**. Study therapists will be compensated at their normal National Deaf Therapy (NDT) reimbursement rate and will take on professional liability for their cases.

- Participants residing in a **state served by NDT** will be **randomly assigned** to receive the experimental *Seeking Safety* + *Signs of Safety* intervention or therapy as usual (TAU). During study start-up, our team will support and fund NDT therapists to seek additional state licensures to ensure that each NDT state has at least one therapist available to provide *Seeking Safety* + *Signs of Safety* and one therapist available to provide TAU. Therapists will *not* cross over between study conditions.

- Participants in states with **no NDT therapists** and who prefer to be placed on NDT's waitlist instead of being referred outside of NDT (currently comprised of 200 individuals) will be **automatically assigned** to the **no-treatment control.** Additional detail about this condition is located below.

Experimental condition: *Seeking Safety* + *Signs of Safety* toolkit. Experimental participants will be offered 12 one-hour, weekly individual therapy sessions of *Seeking Safety* delivered with the *Signs of Safety* toolkit. Sessions will occur virtually via NDT's secure HIPAA-compliant video chat platform. Length of treatment is limited to six months; number of completed sessions will be tracked as a measure of participant adherence.

Feasibility Findings: Prior to the *Signs of Safety* pilot feasibility RCT, we reduced our experimental intervention from 25 to 12 core sessions to fit within a feasible timeframe for clinical research and for practicality of future implementation in community-based practice. This decision was made in consultation with *Seeking Safety's* developer, Dr. Najavits, and is further supported by a NIAAA-funded RCT that showed efficacy of a 12-session, partial-dose *Seeking Safety* for reducing alcohol use frequency.[1]

Active comparison condition: Treatment as usual. Participants assigned to the active comparison condition will receive therapy as usual - i.e., general, open-ended, non-manualized supportive counseling provided by an NDT therapist. In the absence of any evidence-based therapies available for Deaf clients, this unstructured therapy approach is the current standard of care in the field of Deaf mental health. All NDT therapists are Deaf, fluent in ASL, and specialize in issues common to Deaf individuals seeking mental health care. NDT therapists come from a wide variety of training backgrounds, but each works with their clients to build on their existing strengths and provide support as clients develop new strategies and behaviors for overcoming adversity. Like the experimental condition, participants will receive 12 one-hour, weekly individual therapy sessions via NDT's secure virtual therapy platform. Length of treatment is limited to six months; number of completed sessions will be tracked as a measure of participant adherence.

Control condition: No treatment. Participants in states with no NDT therapists and who prefer to be placed on NDT's waitlist instead of being referred outside of NDT for therapy will be automatically assigned to the no-treatment control condition. At the time of this submission, there are approximately 200 individuals on the NDT waitlist; individuals remain on the waitlist until a licensed therapist from their state joins the NDT team.

Participants in the control condition will be prompted to complete assessments at baseline, week 6, week 12 (to approximate immediate post-treatment), week 25 (to approximate three-month follow-up), and week 38 (to approximate six-month follow-up). Such repeated assessment in the control arm will allow us to quantify and control for participants' natural change over time and any potential assessment reactivity.

Feasibility Findings/Alternate Designs Considered: In the *Signs of Safety* randomized feasibility pilot, we tested an artificial waitlist as our control condition. Seventeen percent of eligible participants chose not to enroll in the study because they were motivated for treatment at the time of screening, needed immediate treatment, and would not risk the chance of being placed on a four-month waitlist. Of enrolled participants who were assigned to the waitlist condition, only 57% took advantage of the 12 free sessions of treatment after the four-months waiting period, suggesting that we missed the critical opportunity to intervene at a transitory moment of readiness for change. Given that the proposed study protocol is one year in length (maximum 6-month treatment period + 6-month post-treatment follow-up period), it is ethically unfathomable to create an artificial waitlist and ask that participants refrain from much-needed treatment during this extended period of time. As such, we will use NDT's natural waitlist to feed the proposed control condition. Control participants who gain access to treatment during the study protocol (i.e., come off of NDT's waitlist or gain access to formal psychotherapy elsewhere) will be removed from the study at the point of treatment initiation (see **Section 6.5 Concomitant Therapy** for additional detail).

6.1.2 ADMINISTRATION AND/OR DOSING

Experimental condition: *Seeking Safety* + *Signs of Safety* toolkit. 12 one-hour, weekly individual therapy sessions of *Seeking Safety* delivered with the *Signs of Safety* toolkit.

Active comparison condition: Treatment as usual. Like the experimental condition, participants will receive 12 one-hour, weekly individual therapy sessions.

Control condition: No treatment. N/A - no treatment, assessment only.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

We will **train eight study therapists** from National Deaf Therapy in how to provide *Seeking Safety* + *Signs of Safety*. In the second half of Year 1, consultant Najavits or one of her Treatment Innovations associates will provide a full-day training seminar on how to conduct *Seeking Safety.* Subsequently, PI Anderson and consultant Butland will train therapists in how to add on the *Signs of Safety* toolkit to the

Seeking Safety protocol using a formal didactic training seminar and supervision program. The culmination of the training program will be *Seeking Safety* certification, overseen by Treatment Innovations. Study therapists will be paid their hourly therapy rate and will be provided with CEUs to compensate for time spent in training.

Study therapist credentials include independent licensure in mental health counseling, psychology, or clinical social work; ASL fluency; and experience with addiction and trauma treatment. Of the 15 therapists currently employed by National Deaf Therapy, all meet these criteria. Eight of these 15 therapists are interested in becoming *Seeking Safety* + *Signs of Safety* certified for the proposed trial.

Therapist performance will be evaluated via a structured program of **fidelity monitoring**, including ongoing ratings of experimental session videos and a data-driven supervision group. For each experimental participant, two out of 12 sessions (approximately 96 sessions; 16.7%) will be randomly selected for screen recording. We will capture fidelity throughout the treatment course by randomly selecting one session from sessions 1 - 6 and one session from sessions 7 - 12. Study therapists will be compensated for the time required for video processing and uploading to UMass Chan's secure MoveIt file transfer system.

Session videos will be rated for fidelity on an ongoing basis by consultant Butland, who will be trained and certified as a *Seeking Safety* fidelity rater and supervisor during Year 1 (**Table 1**). Sessions will be rated with the *Seeking Safety Adherence Scale.*[84] Fidelity results will be reviewed on an ongoing basis to identify common challenges to implementation across study therapists; these results will drive discussion topics for a monthly supervision group, which will be co-facilitated by PI Anderson and consultant Butland.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants residing in one of the **21 states served by NDT** will be **randomly assigned** to receive the experimental *Seeking Safety* + *Signs of Safety* intervention or therapy as usual (TAU). During study start-up, our team will support and fund NDT therapists to seek additional state licensures to ensure that each NDT state has at least one therapist available to provide *Seeking Safety* + *Signs of Safety* and one therapist available to provide TAU. Therapists will *not* cross over between study conditions.

The PI and all Co-Is will be masked to study condition.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

For both active treatment conditions, length of treatment is limited to six months; number of completed sessions (out of a possible total of 12 sessions) will be tracked as a measure of participant adherence.

6.5 CONCOMITANT THERAPY

Participants in all study conditions will be asked to refrain from concurrent formal psychotherapy. Participants who engage in formal psychotherapy outside of the research will be removed from the study at the point of treatment initiation. Outside treatment engagement will be queried at each assessment timepoint. If endorsed, the participant will be removed from the study at that timepoint, but data collected prior to treatment initiation will remain in the dataset. Aligning with the *Seeking Safety* model, AA/NA/DRA attendance will be encouraged; attendance will be tracked as a potential outcome mediator. Additionally, medication use for psychiatric conditions and substance use will be tracked as a potential outcome mediator.

6.5.1 RESCUE THERAPY

If at any time a participant is identified as having a serious psychiatric or substance use problem that requires a higher level of care than our study can provide, this concern will be immediately reported to the PI, who will provide referral and bridging to appropriate treatment options for stabilization. Once stabilized, the participant has the option to return to our study. Additional detail is located in **Section 7.**

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Given the proposed study's classification as an NIH-defined Stage III clinical trial, this project will involve oversight from a Data Safety and Monitoring Board (DSMB). UMass Chan Medical School (UMass Chan) has a Population & Quantitative Health Sciences Department that provides DSMB services to University investigators, and we will utilize these services for the proposed trial. Specifically, Co-I Barton, Biostatistician, will oversee the preparation of the DSM report, and he will present that report at DSMB meetings held every year until the end of data collection. The DSMB will be composed of three UMass Chan faculty unaffiliated with the project (e.g., a psychiatrist, an internal medicine physician, and a statistician/epidemiologist). The DSM report will include 1)participants' sociodemographic characteristics; 2) expected versus actual recruitment rates; 3)any quality assurance or regulatory issues that occurred during the past year; 4) a summary of adverse events; and 5) any actions or changes with respect to the protocol. The DSM report will also include, when available, the results of any data analyses. The DSMB Reports will present data from blinded treatment groups. No interim analyses are planned for this study unless the DSMB requests an interim analysis assessment of study efficacy or futility. An independent statistician will prepare any interim analyses requested by the DSMB. The DSMB can request other data in the form of tables, listings, and figures as it determines the necessity to review other information. The DSMB will provide recommendations to NIAAA for the continuation or cessation of the study based on their review of the data.
In addition to the oversight of the DSMB, the PI, a licensed clinical psychologist, will be responsible for monitoring the safety of this trial, executing the NIAAA-approved Data and Safety Monitoring Plan (DSMP), and complying with all reporting requirements. Diligent safety monitoring will be conducted throughout the study as follows:

- Individual data will be monitored by the PI, Co-I Wilkins, and the study therapists over the course of the study to identify any participants who may need additional intervention. Data sources include (1) frequency and quantity of weekly alcohol and drug use collected at the beginning of each therapy session during a structured check-in process; (2) suicidal thoughts, plans, or intent assessed during the structured check-in if the participant reports feelings of depression; (3) check-out process at the end of each therapy session that asks participants if any problems arose for them during the session; (4) PTSD symptoms and alcohol use data collected at five outcome assessment timepoints across the study.

- After each assessment time point, the PI and/or Co-I Wilkins will review data to determine if any particular participants are reporting significant clinical deterioration (i.e., "clinically meaningful" increase of 10+ points on the *PTSD Checklist for DSM-5*, increase in AUD category of severity based on DSM-5 criteria). Should a participant be identified as experiencing significantly worsening distress over the course of the study, the PI will determine the appropriate course of action (e.g., withdrawal from the study and referral to outside treatment). Once stabilized, the participant would have the option to return to our study.

- If at any time a participant is identified as having a serious psychiatric or substance use problem that requires a higher level of care than our study can provide, this concern will be immediately reported to the PI, who will provide referral and bridging to appropriate treatment options for stabilization. Once stabilized, the participant has the option to return to our study.

- Should a participant communicate distress and intent to withdraw from the study, the PI will provide referral and bridging to appropriate treatment options.

- Study therapists will assess withdrawal symptoms on an as-needed basis (e.g., if participants report abrupt alcohol discontinuation) using the *Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)*. Therapists will be instructed to discuss any concerns regarding withdrawal immediately with Co-I Jefee-Bahloul, Addiction Psychiatrist, who will be available for on-call phone consultation.

- Should a participant arrive at a virtual therapy session under the influence of drugs or alcohol, the study therapist will be trained to assess the participant's level of safety, discontinue the session, and reschedule the visit for a later date.

- Study therapists will be trained to follow written protocols and contact 911 in the event of a dangerous situation. The PI will also be available for on-call phone consultation for less urgent clinical crises. The PI will intervene if at any time a participant's distress cannot be contained or in cases where anyone appeared truly unsafe (suicidal intent, threatening harm, or other unsafe behavior). Although it is anticipated that this reaction is highly unlikely, should it occur, the PI will provide debriefing and, if needed, will call for assistance.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

It is unlikely that we will need to withdraw participants from the study. Participants will only be withdrawn if they pose harm to themselves or others (i.e., physical aggression, verbal threats). Although this reaction is highly unlikely, should it occur, the PI would debrief the participant and provide referral to crisis or therapy services outside of the research study as needed. In the event that a participant is found to pose imminent harm to themselves or others, as independently licensed mental health providers, the study therapists will implement any actions required by state law with regard to individuals who are determined to pose imminent harm to themselves or others. Available data collected prior to withdrawal will be included in statistical analyses, unless the participant revokes consent during the withdrawal process.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if they fail to return for 3 consecutive scheduled visits and study staff are unable to contact the participant after at least 3 attempts.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The research team will attempt to contact the participant, reschedule the missed visits, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the research team will make every effort to regain contact with the participant (where possible, 3 calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study on the date of the third missed visit with a primary reason of loss to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

ELIGIBILITY SCREENING

Interested individuals will be sent a link to our eligibility screening survey via email or text. The screening survey will include self-report items for the inclusion and exclusion criteria outlined in **Section 5**, as well as the AUD Identification Test (AUDIT) and PTSD Checklist for DSM-5 (PCL-5). All screening items will be formally translated into ASL and uploaded into our Deaf-accessible REDCap survey (like our outcome measures described below).

MEASURES

Using measures validated in the general population and formally translated into ASL, we will assess clinical outcomes and mechanisms of change at five timepoints: baseline, mid-treatment/week 6, immediate post-treatment/week 12, three-month post-treatment follow-up/week 25, and six-month post-treatment follow-up/week 38. We will report the internal consistency of the newly translated study measures when administered within our national Deaf sample.

At each timepoint, we will prompt participants to complete study measures via our Deaf-accessible REDCap survey. To increase the probability of retention in the assessment protocol, participants will receive stepwise increases in compensation: $50 for baseline, $75 for mid-treatment/week 6, $100 for end-of-treatment/week 12, $125 for three-month follow-up, and $150 for six-month follow-up. We will continue to prompt participants not retained in treatment for outcome information to enable the participant to contribute to intent-to-treat analyses and examine potential biases due to non-adherence.

Feasibility Findings: Exit interviews with *Signs of Safety* participants revealed high levels of perceived burden with study assessment. Participants felt that the number of questions was excessive and many items were repetitive. We have carefully redesigned our test battery to retain only those measures that are absolutely necessary. Our resulting battery of assessments includes 109 questions at each timepoint, with the exception of the end-of-treatment timepoint, which includes an additional 12 items on client satisfaction for those enrolled in treatment arms. Our shift to an online survey platform will further reduce participant burden by eliminating the need to schedule an assessment session and interact with a study assessor.

Measures of **clinical outcome** (listed in table 3 below) are the *Alcohol Timeline Followback,*[29] to assess daily drinking frequency and quantity for a selected time range (we will use “past 30 days” at baseline and “time since last assessment” for all other timepoints); the *Timeline Followback – Drugs, Cigarettes, and Marijuana,* which we will use to assess frequency and quantity of drug use for the same referent time period; the *DSM-5 AUD Assessment Tool,* to track AUD symptoms over time; the *Short Inventory of Problems Revised,* to assess alcohol-related consequences; two items querying alcohol and drug craving from the *Brief Addiction Monitor – Revised*; the *PTSD Checklist for DSM-5,*[30] a measure of DSM-5 PTSD symptoms that is reliably used to monitor symptom change;[75] and the *Outcome Questionnaire (OQ-30.2) for Adults*, to assess changes in psychosocial functioning over time.

We identified potential mechanisms of change from the *Seeking Safety* literature, alcohol treatment literature, and Deaf mental health literature. One key moderator is **motivation for treatment**.[85,86,87] Potential mediators are participants' reported ability to use **coping skills**,[40,80,88,89] practice **self-compassion**,[80,90,91,92] and **understand health information**.[24,35,36,37,58] These constructs will be measured by the *Contemplation Ladder,*[93,94] a single-choice, visual analogue scale whose higher rungs represent greater levels of readiness to change; the *Brief Resilient Coping Scale,*[95,96] a measure of perceived ability to effectively use coping strategies in flexible, committed ways to actively solve problems despite stressful circumstances; the *Self-Compassion Scale – Short Form,*[97] a measure of self-compassion in instances of perceived failure, inadequacy, or suffering; and, the *Ask, Understand, Remember Assessment (AURA),*[98] a measure of one's ability to obtain, understand, and remember health information communicated by a provider.

A measure of client satisfaction will be administered to those participants assigned to active treatment arms. The *Satisfaction with Therapy and Therapist Scale* is a 12-item measure that assesses patients' level of satisfaction with their therapeutic experiences.

Table 3: Clinical Outcome Measures

Domain	Measure (**bold** = *primary outcome*)	# of items
Alcohol and Drug Use	*AUD Identification Test*	10
	Alcohol Timeline Followback	4
	DSM-5 AUD Assessment Tool	13
	Timeline Followback – Drugs, Cigarettes, and Marijuana	5
	Short Inventory of Problems Revised	17
	Alcohol and drug craving items from the Brief Addiction Monitor – Revised	2
PTSD and Psychosocial Functioning	***PTSD Checklist for DSM-5***	20
	Outcome Questionnaire (OQ-30.2) for Adults	30
Mediators and Moderators of Change	*Contemplation Ladder*	1
	Brief Resilient Coping Scale	4
	Self-Compassion Scale – Short Form	12
	Ask, Understand, Remember Assessment	4
Satisfaction	*Satisfaction with Therapy & Therapist Scale*	12

8.2 SAFETY ASSESSMENTS

Assessment and management of withdrawal risk. Study therapists will be trained to have a low threshold for alcohol withdrawal risk. For any participants reporting alcohol discontinuation, study therapists will ask participants if they are experiencing any significant symptoms of withdrawal - tremors, sweating, flushing, nausea, vomiting, hallucinations, or seizures. If a participant endorses any of these symptoms, the therapist will briefly pause the session to consult with Co-I Jefee-Bahloul, Addiction Psychiatrist, who will be available for on-call phone consultation. Given the potential lethality of alcohol withdrawal, Dr. Jefee-Bahloul will likely recommend voluntarily sending the participant to detox or the Emergency Department for evaluation (Note: Prior to study initiation, our team will work with National Deaf Therapy to identify detox programs in each state where study intervention will be provided). Following the therapy session, the therapist will report the event to PI Anderson.

Identification of serious psychiatric problem. If at any time a participant is identified as having a serious psychiatric problem that requires a higher level of care than our study can provide, this concern will be immediately reported to PI Anderson, who will work with NDT referral specialists to identify appropriate local treatment options for stabilization. Once stabilized, the participant will have the option to return to our study.

Clinical emergencies. For risk concerns, like suicidality, study therapists will follow established NDT protocols. This protocol includes (1) clear communication on the therapy request form that NDT is not a crisis center; (2) a structured Suicide Risk Assessment performed during the intake process; (3) a Telehealth Emergency Consent form that all clients/participants review and sign (see embedded form below); and (4) development of a safety plan for all clients/participants. Study therapists will contact 911 in the event of a dangerous situation (or the PI for less urgent clinical crises) and will complete adverse events reports.

Deterioration. The definition of clinical deterioration, i.e., worsening of AUD or PTSD symptoms, and detailed steps to be taken are outlined in the **NIAAA Data and Safety Monitoring Plan**. In the event of deterioration, the study therapists will consult with PI Anderson to determine the appropriate course of action.

4. ***TELEMENTAL HEALTH & EME

NATIONAL DEAF THERAPY, LLC

CONSENT FOR TELEHEALTH CONSULTATION

- ☐ I understand that my health care provider wishes me to engage
- ☐ My health care provider explained to me how the video confere a consultation will not be the same as a direct client/health care the same room as my provider.
- ☐ I understand that a telehealth consultation has potential benefit convenience of meeting from a location of my choosing.
- ☐ I understand there are potential risks to this technology, includi technical difficulties. I understand that my health care provider is felt that the videoconferencing connections are not adequate
- ☐ I have had a direct conversation with my provider, during which to this procedure. My questions have been answered and the ri been discussed with me in a language in which I understand.

CONSENT TO USE THE TELEHEALTH BY THERA

By signing this form, I certify:

That I have read or had this form read and/or had this form explain

That I fully understand its contents including the risks and benefits

That I have been given ample opportunity to ask questions and tha
satisfaction.

Emergency Procedures Specific to Telehealth Ser

There are additional procedures that we need to have in place spe
safety in case of an emergency and are as follows:

In Case of an Emergency

If you have a mental health emergency, we encourage you not to w
but do one or more of the following:

You understand that if you are having suicidal or homicidal thought
crisis that we cannot solve remotely, we may determine that you ne
are not appropriate. we require an Emergency Contact Person (EC
threatening emergency only. Please enter this person's name and

Either you or we will verify that your ECP is willing and able to go t
Additionally, if either you, your ECP, or we determine necessary, th
signature at the end of this document indicates that you understan
extreme circumstances stated above.

Please list your Emergency Contact Person here (NAME, ADDRES

You agree to inform us of the address where you are at the beginn
the nearest mental health hospital to your primary location that you
emergency

☐ BY CLICKING ON THE CHECKBOX, I AM AGREEING THAT I
THE ITEMS CONTAINED IN THIS DOCUMENT.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, **whether or not considered intervention-related.**

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Results in death, is life threatening, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability/incapacity, or any other event that may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

The PI will distinguish a serious adverse event (SAE) from a non-serious adverse event (AE) and provide attributions (causality and severity) using the definitions below as a guide. If needed, the PI will consult with the DSMB and/or UMass Chan Institutional Review Board for assistance and clarification.

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe the severity of adverse events (AEs) not included in the protocol-defined grading system:

- **Mild:** Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate:** Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

- **Unrelated:** There is not a reasonable possibility that the adverse event may have been caused by participation in the study.
- **Possibly related:** The adverse event may have been caused by participation in the study; however, there is insufficient information to determine the likelihood of this possibility.

- **Related:** There is a reasonable possibility that the adverse event may have been caused by participation in the study.

8.3.3.3 EXPECTEDNESS

- **Expected/anticipated:** Identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.
- **Unexpected/unanticipated:** Not identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Any SAE, unanticipated problems, or breaches of confidentiality that occur during the study will be reported to the UMass Chan Institutional Review Board and the NIAAA project officer within 48 hours. The initial report will include a brief description of the situation and when it occurred. This report will be followed up with a written report no more than 72 hours later.
The PI will develop follow-up plans for SAE and unresolved unanticipated problems in collaboration with the UMass Chan Institutional Review Board.
Detailed guidance on reportable events can be found in UMass Chan Institutional Review Board HRP-801: INVESTIGATOR GUIDANCE: Prompt Reporting Requirements:
https://www.umassmed.edu/globalassets/ccts/ccts-media/irb/investigator-guidance-2015/hrp-801-investigator-guidance---prompt-reporting-requirements.umass.pdf

8.3.5 ADVERSE EVENT REPORTING

An annual report will be submitted to the NIAAA project officer summarizing all adverse events. When completing the annual report, the PI will include a summary of all adverse events, confirmation of adherence to the DSMP, a summary of any data and safety monitoring issues since the prior reporting period, a description of the changes in the research protocol or DSMP, and all new and continuing IRB approvals. The annual DSMB report will also be forwarded to the NIAAA project officer, including listings and summary of all AEs and SAEs

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Any SAE, unanticipated problems, or breaches of confidentiality that occur during the study will be reported to the UMass Chan Institutional Review Board and the NIAAA project officer within 48 hours. The initial report will include a brief description of the situation and when it occurred. This report will be followed up with a written report no more than 72 hours later. The follow-up report will include a) the date of the event, b) further description, c) actions taken by project staff, d) study condition, e) planned follow-up (if any), f) whether the event appears related to the study, and g) whether it will affect further participation.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

We will not knowingly include pregnant women as participants; however, we will not assess participants' pregnancy status.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("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); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The PI will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to NIAAA. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the NIAAA Project Office within 48 hours of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the NIAAA Project Office within 48 hours of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the NIAAA Project Office, and the Office for Human Research Protections (OHRP) within 72 hours of the IRB's receipt of the report of the problem from the investigator

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint(s):
We will compare study conditions using two primary clinical outcomes at immediate post-treatment and follow-up: (1) past 30-day alcohol use frequency/quantity (from the *Alcohol Timeline Followback*[28]) and (2) past 30-day PTSD severity (from the *PTSD Checklist for DSM-5*[29]).

Alcohol use outcomes are: % drinking days per week (i.e., days with 1+ drink); % binge drinking days per week (i.e., days with 5+ drinks for men, 4+ for women); and mean number of drinks per drinking day. We will calculate these variables from daily data collected with the *Alcohol Timeline Followback* for 30 days prior to baseline assessment and, for all additional timepoints, the time to last assessment timepoint.

The primary **PTSD outcome** is total symptom severity on the *PCL-5.* We will compare individual achievement of a 10-point decrease in the *PCL-5* at each post-baseline timepoint (as a binary outcome) using a generalized estimating equations (GEE) longitudinal logistic model.

Secondary Efficacy Endpoint(s):
We will examine potential moderators and mediators of intervention effects (Table 3). We will classify baseline factors (e.g., stable patient characteristics, motivation for treatment) as moderators and intervention-related factors as mediators, such as coping skills, self-compassion, and understanding of health information. We will use forest plots in the subgroup analyses to display the treatment effects (and 95% confidence intervals) without statistical inference.

Table 3: Clinical Outcome Measures

Domain	Measure (**bold** = *primary outcome*)	# of items
Alcohol and Drug Use	*AUD Identification Test*	10
	Alcohol Timeline Followback	4
	DSM-5 AUD Assessment Tool	13
	Timeline Followback – Drugs, Cigarettes, and Marijuana	5
	Short Inventory of Problems Revised	17
	Alcohol and drug craving items from the Brief Addiction Monitor – Revised	2
PTSD and Psychosocial Functioning	***PTSD Checklist for DSM-5***	20
	Outcome Questionnaire (OQ-30.2) for Adults	30
Mediators and Moderators of Change	*Contemplation Ladder*	1
	Brief Resilient Coping Scale	4
	Self-Compassion Scale – Short Form	12
	Ask, Understand, Remember Assessment	4
Satisfaction	*Satisfaction with Therapy & Therapist Scale*	12

9.2 SAMPLE SIZE DETERMINATION

Based on preliminary data from the *Signs of Safety* open pilot and pilot RCT, we predict that 108 of 144 enrolled participants will complete the end-of-treatment assessment (conservative retention rate of 75%), or 36 participants per study arm. The proposed follow-up periods for the present study exceed the *Signs of Safety* R34's one-month follow-up period; therefore, we are unable to project the number of participants who will complete three-month and six-month follow-up assessments.
A clinically significant effect was used for the current power calculation. Specifically, a clinically significant change score for the *PCL-5* is 10 points for an individual.[65] Our projected sample size of 36 completers per study arm will have over 80% power to detect an increase in the percentage of participants in the intervention group who achieve a decrease of 10 points in the *PCL-5* to 36% compared to an estimated 10% in the control group using an unadjusted likelihood ratio chi-square test with a two-sided alpha = 0.05. In the analysis described in section 9.4, we will use a longitudinal logistic model to adjust the treatment effect for other factors, such as gender and race. Because we do not have good estimates of the correlation among the measures of the *PCL-5* among participants over time, we used the more conservative likelihood ratio chi-square for sample size estimates but expect the longitudinal models to have more power and, thus, be able to detect smaller differences due to the partitioning of the variance among the various components.

9.3 POPULATIONS FOR ANALYSES

- Per Protocol Population: Participants who receive all 12 sessions of their assigned treatment and complete the Week 12/Post-Treatment assessment.
- Minimum Dose Population: Participants who receive at least 6 sessions of their assigned treatment and complete the Week 12/Post-Treatment assessment.
- Intent-to-Treat Population: Participants who receive at least 1 session of assigned treatment and complete the Week 12/Post-Treatment assessment. Patients will be analyzed in the treatment group to which they were randomized.
- Safety Analysis Dataset: All participants in the sample who receive at least one treatment session or participate in at least one assessment time point (after baseline assessment). Patients will be analyzed based on the treatment that they actually received.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Data will be entered into REDCap, a secure web-based data capture application that provides real-time data entry validation (e.g., data types, range checks).[89,90] Our team's senior database developer will customize the database to track recruitment, intervention delivery, and outcome assessments. Data will be exported to *SAS* for analysis.

Details of the statistical analyses will be contained in the Statistical Analysis Plan (SAP) to be developed prior to the first DSMB meeting.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

We will compare study conditions using two primary clinical outcomes at immediate post-treatment and follow-up: (1) past 30-day alcohol use frequency/quantity (from the *Alcohol Timeline Followback*[28]); and (2) past 30-day PTSD severity (from the *PTSD Checklist for DSM-5*[29]).

Alcohol use outcomes are: % drinking days per week (i.e., days with 1+ drink); % binge drinking days per week (i.e., days with 5+ drinks for men, 4+ for women); and mean number of drinks per drinking day. We will calculate these variables from daily data collected with the *Alcohol Timeline Followback* for 30 days prior to baseline assessment and, for all additional timepoints, the time to last assessment timepoint.

For our initial unadjusted group comparisons at immediate post-treatment/week 12, at the end of the three-month post-treatment follow-up/week 25, and at the end of the six-month post-treatment follow-up/week 38, will use a standard t-test (or Wilcoxon non-parametric test, depending on the outcome distribution). Below, we describe models for analyzing adjusted group differences and for analyzing the longitudinal data.

We will use separate generalized estimating equations (GEE) models for each alcohol-use outcome as predicted by study condition, patient characteristics, clinician characteristics, and the time metric (baseline, week 6, week 12, week 25, and week 38). Part of our analysis will use two-level GEE models with participants nested within clinician/therapist. These models will also include the demographics and characteristics of the clinicians and participants to investigate the effects of those factors on the outcomes of that Aim. The GEE model will effectively handle the intra-clinician correlation among the participants who are assigned to each clinician. Because of the uncertainty of the magnitude of the intra-clinician correlation, we did not include an adjustment in the sample size estimation. As a sensitivity analysis, we will also use mixed effects models with repeated measures (MMRM), including random intercepts due to the expected baseline variability and participants as random effects to adjust for unmeasured covariates. From this model, we can generate custom comparisons for changes from baseline to each of the other timepoints and between the timepoints to estimate the change from post-intervention as an indicator of retention of the intervention effect. In the mixed effects model, we will initially assume an unstructured correlation structure, but, if there are convergence problems, we will try other structures such as AR(1), heterogeneous AR(1), Toeplitz, and heterogeneous Toeplitz. We will also investigate if the study conditions exhibit different variance-covariance matrices, requiring different

R-side specifications. We will compare the GEE results with the MMRM results to identify any differences, requiring deeper analyses to determine the cause.

The primary **PTSD outcome** is total symptom severity on the *PCL-5.* We will compare individual achievement of a 10-point decrease in the *PCL-5* at each post-baseline timepoint (as a binary outcome) using a GEE longitudinal logistic model. Predictors are study condition, timepoint (baseline as the reference group), and interaction of study condition. As logistic models are sensitive to the number of predictors relative to the number of positive outcomes, we will add other predictors to the model while monitoring for overfitting. Possible predictors are participant and clinician characteristics and baseline *PCL-5* score. Although the sample size is relatively small, limiting the use of interaction terms, we will use forest plots to illustrate treatment effects in subgroups of participants, as suggested by the FDA.[91]

Handling missing data. Analyses will be conducted as **intent-to-treat**, with all participants assigned to a study condition included in the analysis regardless of treatment adherence or missing data in any timepoints. We will use the GEE procedure in *SAS* to analyze the longitudinal data by fitting the models described above – a procedure that allows for data that are missing at random by including all available data from each participant in the analysis. In the event that a participant has no available outcome data, we will examine their sociodemographic characteristics to compare with those participants who do have available outcome data. For outcomes with **missing** data, we will first determine if the data are missing at random (MAR) or missing not at random (MNAR), using a logistic model to identify predictors related to missingness. If none of the predictors are significantly related to missingness, we will assume that the data are MAR and will use multiple imputation to monotonically complete the data set. We will impute the missing data using a predictive model for the same treatment group as the participant with missing data. If the data are MNAR, we will initially use stratified models to obtain separate sets of results for each category of the variable that indicates MNAR. Other strategies to control the MNAR problem will depend on the exact nature of the MNAR.

Multiplicity. To control the family-wise error rate (FWER) for this study, we will use a gatekeeping approach.[92] The primary outcome, *PCL-5* total symptom severity, will be tested at the two-sided alpha = 0.05 level as indicated above. If the proportion of participants achieving a decrease of 10 points or greater in the intervention group is significantly greater than for the control group, we can recycle the alpha error to test the secondary outcome (alcohol-use frequency) at the same level. The other outcomes will be tested as supportive (but not binding) outcomes, reporting group comparisons (and p-values) as descriptive information.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary outcomes are the Timeline Followback – Drugs, Cigarettes, and Marijuana, which we will use to assess frequency and quantity of drug use for the same referent time period; the DSM-5 AUD Assessment Tool to track AUD symptoms over time; the Short Inventory of Problems Revised, to assess alcohol-related consequences; two items querying alcohol and drug craving from the Brief Addiction Monitor – Revised; and the Outcome Questionnaire (OQ-30.2) for Adults, to assess changes in psychosocial functioning over time.

We identified potential mechanisms of change from the Seeking Safety literature, alcohol treatment literature, and Deaf mental health literature. One key moderator is motivation for treatment .[74,75,76] Potential mediators are participants' reported ability to use coping skills,[39,72,77,78] practice self-compassion,[72,79,80,81] and understand health information.[23,34,35,36,58] These constructs will be measured by the Contemplation Ladder,[82,83] a single-choice, visual analogue scale whose higher rungs represent greater levels of readiness to change; the Brief Resilient Coping Scale,[84,85] a measure of perceived ability to effectively use coping strategies in flexible, committed ways to actively solve problems despite stressful circumstances; the Self-Compassion Scale – Short Form,[86] a measure of self-compassion in instances of perceived failure, inadequacy, or suffering; and, the Ask, Understand, Remember Assessment (AURA),[87] a measure of one's ability to obtain, understand, and remember health information communicated by a provider.

The analysis of each of these outcomes will be described in detail in the SAP developed prior to the first DSMB meeting.

9.4.4 SAFETY ANALYSES

In addition to the oversight of the DSMB, the PI, a licensed clinical psychologist, will be responsible for monitoring the safety of this trial, executing the NIAAA-approved Data and Safety Monitoring Plan (DSMP), and complying with all reporting requirements. Diligent safety monitoring will be conducted throughout the study as follows:

- Individual data will be monitored by the PI, Co-I Wilkins, and the study therapists over the course of the study to identify any participants who may need additional intervention. Data sources include: (1) frequency and quantity of weekly alcohol and drug use collected at the beginning of each therapy session during a structured check-in process; (2) suicidal thoughts, plans, or intent assessed during the structured check-in if the participant reports feelings of depression; (3) check-out process at the end of each therapy session that asks participants if any problems arose for them during the session; (4) PTSD symptoms and alcohol use data collected at five outcome assessment timepoints across the study.

Safety endpoints:

- **Identification of serious psychiatric problem.** If at any time a participant is identified as having a serious psychiatric problem that requires a higher level of care than our study can provide, this concern will be immediately reported to PI Anderson, who will work with NDT referral specialists to identify appropriate local treatment options for stabilization. Once stabilized, the participant will have the option to return to our study.

- **Clinical emergencies.** For risk concerns, like suicidality, study therapists will follow established NDT protocols. This protocol includes: (1) clear communication on therapy request form that NDT is not a crisis center; (2) structured Suicide Risk Assessment performed during the intake process; (3) Telehealth Emergency Consent form that all clients/participants review and sign (see attached); and (4) development of a safety plan for all clients/participants. Study therapists will contact 911 in the event of a dangerous situation (or the PI for less urgent clinical crises) and will complete adverse events reports.

- After each assessment time point, the PI and/or Co-I Wilkins will review data to determine if any particular participants are reporting significant clinical deterioration (i.e., "clinically meaningful" increase of 10+ points on the *PTSD Checklist for DSM-5*, increase in AUD category of severity based on DSM-5 criteria). Should a participant be identified as experiencing significantly worsening distress over the course of the study, the PI will determine appropriate course of action (e.g., withdrawal from study and referral to outside treatment). Once stabilized, the participant would have the option to return to our study.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline data will include participant demographics and selected characteristics relevant to the study. For reporting to the DSMB (and for Table 1 in publications), we will generate a table (or potentially comparative bar charts) of these demographics and characteristics with summary statistics for each item by treatment group. For binary or categorical variables, such as biological sex (male/female) or age group (e.g., 18-35, 36-50,, etc.), we will present proportions of the participants in that group with that characteristic with the column adding up to 1.0 or 100% and the associated number n for that proportion. For continuous variables that are normally distributed (verified by the Wilk-Shapiro test of normality), we will present the number of participants with that measure (n), mean, and standard deviation. For continuous variables that are not normally distributed, we will present the median and inter-quartile range (IQR). If the standard deviations are markedly different, we will present comparative box plots to understand the distribution of the variable and, thus, the best way to present measures of central tendency (i.e., mean, median) and variance (i.e., standard deviation, inter-quartile range). This exploratory analysis (when needed) will also be presented to the DSMB to provide the justification for the chosen method of presentation (and, potentially, analysis).

9.4.6 PLANNED INTERIM ANALYSES

Given the proposed study's classification as an NIH-defined Stage III clinical trial, this project will involve oversight from a Data Safety and Monitoring Board (DSMB). UMass Chan Medical School (UMass Chan) has a Population & Quantitative Health Sciences Department that provides DSMB services to University investigators and we will utilize these services for the proposed trial. Specifically, Co-I Barton, Biostatistician, will oversee the preparation of the DSM report, and he will present that report at DSMB meetings held every year until the end of data collection. The DSMB will be composed of three UMass Chan faculty unaffiliated with the project (e.g., a psychiatrist, an internal medicine physician, and a statistician/epidemiologist). The DSM report will include participants' sociodemographic characteristics, expected versus actual recruitment rates, any quality assurance or regulatory issues that occurred during the past year, summary of adverse events, and any actions or changes with respect to the protocol. The DSM report will also include, when available, the results of any data analyses. The DSMB can request other data in the form of tables, listings, and figures as it determines the necessity to review other information. The DSMB will provide recommendations to NIAAA for the continuation or cessation of the study based on their review of the data.

9.4.7 SUB-GROUP ANALYSES

We will also display the treatment effect by subgroups (the equivalent of the interaction terms) in a forest plot, as recommended by the FDA/EMA for subgroup analyses.[91] The subgroups can be defined for the demographics of clinicians and participants (and both together) as well as the characteristics of

each. In addition to these subgroup analyses, we will explicitly model sex as a biological variable in this research because we expect that the interactions identified in the mediator/moderator analysis described in the application may be substantially different between men and women – and this applies to both clinicians and participants.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

We do not anticipate presenting individual participant data as part of our reporting and analysis, except for SAE data, which will include the specifics of the SAE and the resolution by patient and event. Only Study ID numbers will be used to identify the patient. This information will be contained only in the DSMB reports and any required reports for the NIAAA Project Office and the UMass Chan IRB. All other participant data will be presented as summarized within treatment groups only.

9.4.9 EXPLORATORY ANALYSES

We will examine potential moderators and mediators of intervention effects (Table 3). We will classify baseline factors (e.g., stable patient characteristics, motivation for treatment) as moderators and intervention-related factors as mediators, such as coping skills, self-compassion, and understanding of health information. We will use forest plots in the subgroup analyses to display the treatment effects (and 95% confidence intervals) without statistical inference.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Promptly following screening, eligible individuals will be offered a remote video appointment during which one of our Deaf Community Advisors will conduct **informed consent** procedures. The Deaf Community Advisors will follow HRP-090 SOP: Informed Consent Process for Research.

Prior to the call, the individual will receive an electronic copy of the IRB-approved, written English informed consent form (e-Consent) via REDCap, a HIPAA-compliant, web-based electronic capture database used by UMass Chan. During the call, the Deaf Community Advisor will present each section of the e-Consent form in ASL (e.g., “What are the risks of being in this study?”, “What happens to information about me?”), pausing after each section for questions and discussion. Individuals who wish to enroll will sign the e-Consent form in REDCap, by typing in their name or using the “wet signature” feature.

During the informed consent process, participants will be informed that they have the right to refrain from answering any questions. It will be emphasized that any information provided by the participant is completely voluntary and that they can leave the study at any time if they choose.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The Deaf Community Advisors will follow HRP-091 SOP: Written Documentation of Consent. Individuals who wish to enroll in our study will sign the e-Consent form in REDCap, by typing in their name or using the “wet signature” feature. All study procedures, potential risks, and potential benefits will be explained in detail by the Deaf Community Advisors in ASL prior to obtaining written consent.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the IRB, and the NIAAA project office and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping

- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the NIAAA Project Office, the UMass Chan IRB, and the DSMB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Every effort will be made to protect participants' confidentiality. Only CITI-trained personnel with appropriate authorization and relevant project need will be allowed data access. An NIH Certificate of Confidentiality will protect participants from disclosure of sensitive data, especially information related to substance use. Study therapists will comply with confidentiality policies per the ethical requirements of their independent licensing board (e.g., Board of Registration of Psychologists).

For each experimental participant, two out of 12 intervention sessions will be randomly selected for screen recording (for the purposes of fidelity monitoring). Study therapists will be instructed to immediately upload the recording to UMass Chan's secure MoveIt file transfer system. Once received by the research team, the recording will be transferred to a password-protected file on the secure, password-protected, encrypted, internal, and HIPAA-Compliant server hosted by UMass Chan.

All other study data will be recorded in a REDCap database (REDCap Consortium, Vanderbilt University) in the secure, regulated environment at UMass Chan. This environment and REDCap are only accessible by medical school staff with IRB approval who are assigned an account in this environment by UMass Chan IT. We will program the system for a single entry with validation rules at the time of entry and comprehensive edits conducted after the data have been submitted to the main data base. These edits will check for validity, consistency, and normal range values. Additional edit checks will be performed routinely to identify additional potential errors through multivariable edit approaches. Edit queries will be generated and resolved by research staff with corrections posted to the database through the REDCap system, which enforces an audit trail for all changes. REDCap will also have the audit trail capability enabled for tracing any data modifications.

REDCap will be used within the secure environment to protect any PHI/PII data that are collected as part of the study. We will strive to minimize collection of such sensitive data and REDCap will be programmed to segregate that data from the main study data so that exports for analysis will be deidentified. Data will be exported from REDCap for import into the latest version of *SAS* for all analyses. All reports and analyses will be generated from these files. Data files that are used for reports, presentations, or publication will be archived as required past the end of the study.

All paper records, video recording, and electronic data records will be destroyed three years after completion of the grant period, in accordance with NIH policy, including the master list linking participant code numbers with their identifying data.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

We will submit and share data with the NIAAA Data Archive, a data repository housed within the NIMH Data Archive (NDA), per the requirements set forth in NOT-AA-23-002 (https://grants.nih.gov/grants/guide/notice-files/NOT-AA-23-002.html). All data will be de-identified before submission to the data archive. Additional details can be found in the uploaded document "NIAAA Signs of Safety R01, NIAAA Data Archive Data Sharing Plan, 6.2.2023.docx".

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor or Independent Safety Monitor**
Melissa L. Anderson	Jefee-Bahlou
UMass Chan Medical School	
222 Maple Ave., Chang Building Shrewsbury, MA 01545	
508-856-5820	
melissa.anderson@umassmed.edu	

10.1.6 SAFETY OVERSIGHT

Given the proposed study's classification as an NIH-defined Stage III clinical trial, this project will involve oversight from a Data Safety and Monitoring Board (DSMB). UMass Chan Medical School (UMass Chan) has a Population & Quantitative Health Sciences Department that provides DSMB services to University investigators and we will utilize these services for the proposed trial. Specifically, Co-I Barton, Biostatistician, will oversee the preparation of the DSMB report, and he will present that report at DSMB meetings held every six months until the end of data collection. The DSMB will be composed of three UMass Chan faculty unaffiliated with the project (e.g., a psychiatrist, an internal medicine physician, and a statistician/epidemiologist). The DSMB report will include participants' sociodemographic characteristics, expected versus actual recruitment rates, any quality assurance or regulatory issues that occurred since the last meeting, summary of adverse events, and any actions or changes with respect to the protocol. The DSMB report will also include, when available, the results of descriptive (graphical) analyses of the study outcomes without any statistical testing. The DSMB can request other data in the form of tables, listings, and figures as it determines the necessity to review other information. The DSMB will provide recommendations to NIAAA for the continuation or cessation of the study based on their review of the data.

10.1.7 CLINICAL MONITORING

In addition to the oversight of the DSMB, the PI, a licensed clinical psychologist, will be responsible for monitoring the safety of this trial, executing the NIAAA-approved Data and Safety Monitoring Plan (DSMP), and complying with all reporting requirements.

Study therapists will be trained to have a low threshold for alcohol withdrawal risk. For any participants reporting alcohol discontinuation, study therapists will ask participants if they are experiencing any

significant symptoms of withdrawal - tremors, sweating, flushing, nausea, vomiting, hallucinations, or seizures. If a participant endorses any of these symptoms, the therapist will briefly pause the session to consult with Co-I Jefee-Bahloul, Addiction Psychiatrist, who will be available for on-call phone consultation. Given the potential lethality of alcohol withdrawal, Dr. Jefee-Bahloul will likely recommend voluntarily sending the participant to detox or the Emergency Department for evaluation (Note: Prior to study initiation, our team will work with National Deaf Therapy to identify detox programs in each state where study intervention will be provided). Following the therapy session, the therapist will report the event to PI Anderson.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Study data will be recorded in a REDCap database (REDCap Consortium, Vanderbilt University) in the secure, regulated environment at UMass Chan. This environment and REDCap are only accessible by medical school staff with IRB approval who are assigned an account in this environment by UMass Chan IT. We will program the system for a single entry with validation rules at the time of entry and comprehensive edits conducted after the data have been submitted to the main data base. These edits will check for validity, consistency, and normal range values. Additional edit checks will be performed weekly to identify additional potential errors through multivariable edit approaches. Edit queries will be generated and resolved by research staff with corrections posted to the database through the REDCap system, which enforces an audit trail for all changes. REDCap will also have the audit trail capability enabled for tracing any data modifications.

REDCap will be used within the secure environment to protect any PHI/PII data that are collected as part of the study. We will strive to minimize collection of such sensitive data and REDCap will be programmed to segregate that data from the main study data so that exports for analysis will be deidentified. Data will be exported from REDCap for import into the latest version of *SAS* for all analysis. All reports and analyses will be generated from these files. Data files that are used for reports, presentations, or publication will be archived as required past the end of the study. All research records will be destroyed three years after completion of the grant period, in accordance with NIH policy. Individual data will not be available for release.

Quality assurance of data entry and data management consists of a set of proactive tools that are implemented to increase the quality of the data processing components. Specifically, these include: (1) form design to avoid structural missingness, orphan questions, and as many “write-in” responses as possible; (2) training of the data entry operators on the study forms so that they are familiar with the required responses; (3) design of the data entry screens to look as much like the paper forms as possible; (4) specifications of the data fields to reflect the nature of the data to be entered; (5) specification of the edit parameters and checking algorithms so that every field is verified as completely as possible; and (6) validation of the database system to certify that data entered into the data entry screens are accurately recorded in the databases.

For quality control measures, we will conduct regular analyses to investigate: (1) number of missing data items; (2) number and type of forms that are failing edit; and (3) distribution of data to look for outliers. A Quality Control report will be generated at the same time as the DSMB report for review by study leadership and by the DSMB.

In addition to the quality assurance/quality control plans for data entry described above, we will select a 10% sample of patients to review select (high-risk) data for verification against the source documents, including patient characteristics and laboratory assay results.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The REDCap system will be programmed and maintained by study staff at the UMass Chan; data entry will be performed by the participants themselves by responding to REDCap online surveys.

10.1.9.2 STUDY RECORDS RETENTION

Data files that are used for reports, presentations, or publication will be archived as required past the end of the study. All research records will be destroyed three years after completion of the grant period, in accordance with NIH policy. Individual data will not be available for release.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly. These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the PI to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation, or within 3 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to our NIAAA Program Official and DSMB. Protocol deviations must be sent to the reviewing IRB per their policies. The PI is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As

such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov.
We will submit and share data with the NIAAA Data Archive, a data repository housed within the NIMH Data Archive (NDA), per the requirements set forth in NOT-AA-23-002 (https://grants.nih.gov/grants/guide/notice-files/NOT-AA-23-002.html). All data will be de-identified before submission to the data archive. Additional details can be found in the uploaded document "NIAAA Signs of Safety R01, NIAAA Data Archive Data Sharing Plan, 6.2.2023.docx".

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with UMass Chan Medical School has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board

DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	2/4/2024	Initial Version	Initial version for ClinicalTrials.Gov

11 REFERENCES