Protocol for Phase 3: HaRTC Efficacy RCT

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Phase 3 will comprise a partially nested randomized controlled trial comparing HaRTC and delayed HaRTC on alcohol outcomes, Quality of Life (QoL), and cost-effectiveness. Secondary analyses will test the hypothesized HaRTC effect on American Indian/Alaska Native/Indigenous cultural connectedness and investigate whether this effect mediates the effect of HaRTC on outcomes

Participants

We will enroll 300 AI/ANs with AUDs. Inclusion criteria are a) being urban AI/AN, b) being at least 21 years of age (for legal reasons), c) living in an urban area (RUCA defined) not on Tribal or Reservation land, d) meeting criteria for a current Alcohol Use Disorder (AUD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), e) technological literacy for video conferencing/text. Exclusion criteria are a) refusal or inability to consent to participation in research, and b) potential to place the safety or security of other patients or staff at risk. Based on prior experience, we expect study exclusions to be rare. Ability to consent will be assessed during the information session using the *UCSD Brief Assessment of Capacity to Consent (UBACC)*.[1] This 10-item, 3-point Likert-scale measure ensures participants understand the study protocol, potential risks/benefits and their rights as participants prior to study enrollment

Measures and Materials (see Appendix C)

Measures for tracking/sample description. The *Tracking Information Sheet* will assess participants' contact information to facilitate reminder contacts for future appointments. The *Participant Information Questionnaire (PIQ)* will assess age, sex assigned at birth, gender, race/ethnicity, education, employment, military experience, participation in other research and/or treatment, and experience of homelessness.

Measures of Enculturation. *The Cultural Connectedness Questionnaire* comprises is a 29-item Likert type measure consisting of 3 dimensions: identity, traditions, and spirituality. Criterion validity was demonstrated with cultural connectedness dimensions adequately correlating with other indicators of wellness. The resulting scale scores will represent the proposed mediator in this study.

Measures of alcohol-use outcomes. *The Structured Clinical Interview for the DSM-5 (SCID-5)* is a validated, structured assessment of DSM-5 criteria for psychiatric disorders. The AUD

portion of this measure will be used to document the presence of an AUD, a key criterion for study inclusion. The Alcohol and Substance Use Frequency Assessment items were adapted from the *Addiction Severity Index-Fifth Edition (ASI-5th Ed)* and will be used to assess frequency of alcohol and other drug use in the past 30 days. *The Alcohol Quantity and Use Assessment* was created by the research team for previous studies with a similar population and will be used to record the quantity of alcohol consumed on participants' heaviest, typical, and lightest drinking days in the past month. *The Short Inventory of Problems-2nd Revision* (SIP-2R) is a psychometrically reliable and valid 15-item, Likert-scale questionnaire, measures social, occupational, and psychological problems related to alcohol use. *Ethyl glucuronide (EtG) urine tests* will be used to validate self-reported alcohol use at each assessment. EtG, a metabolite of ethyl alcohol formed in the body after ethanol exposure, reflects alcohol consumption over the previous 72 hours. The EtG cutoff (> 300ng/ml) will serve as a secondary outcome in analyses.

Measures of Health-related Quality of Life (HRQoL). *The EuroQoL-5 Dimensional-5 Level* (EQ-5D-5L) is a standardized 5-item, 5-point Likert scale measure of health-related QoL (HRQoL). This reliable and valid measure comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Measures of criminal justice and health-care system utilization. *The Non-Study Resources Form* documents resource utilization in cost-effectiveness research. It will assess participants' use of non-study medical resources (e.g., medication and inpatient, outpatient, and emergency services) as well as non-medical resources (e.g., travel time to medical care). *The HaRTC Cost Analysis Questionnaire* comprises 9, yes/no and fill-in-the-blank questions assessing participant costs of attending the HaRTC sessions. *The Criminal Justice Utilization Form* comprises 8, yes/no and fill-in-the-blank questions assessing the extent of participants' contact with the criminal justice system (jail, prison, arrests, probation).

Participant satisfaction. *The Participant Satisfaction Assessment* is a semi-structured interview with open-ended questions and prompts to assess participants' receipt of and satisfaction with HaRTC. *The Participant Feedback Form* features Likert-type items that document participants' feedback on HaRTC. Both measures will be administered to HaRTC participants at the post-test session.

Training of research staff

Research ethics and integrity will be addressed in staff training and in weekly supervision. All research staff will complete human subjects and HIPAA training prior to data collection.

Research staff, including bachelor-level research assistants and graduate students, will conduct assessment interviews under the weekly supervision of the Co-PIs, who are clinical psychologists, one with a current WA State license and nearly 25 years of experience conducting substance-use assessment and the other with 10 years of Native health research and assessment. An extensive training protocol developed during a prior evaluation will be utilized.[7] Interviewers will receive 16 hours of training and supervision before they begin independently recruiting and assessing participants. Training will include training in cultural humility and Native health, written instructions (e.g., probe instructions, skip patterns, behavioral problem management) and mock interviews with feedback. Periodic interview observations by lead research staff will occur throughout Phase 3. Circle keepers will be identified and interviewed by HaRTC and SIHB Traditional Health Professionals and will be approved by the Community Advisory Board. They will identify as Indigenous, American Indian, and/or Alaska Native; have a background in Traditional Indian Medicine and/or chemical dependency counseling; have lived experience of substance use disorder; and have a working knowledge of and comfort with a harm-reduction orientation to substance-use treatment. Although they will be proficient and independent in their own practice, they will be introduced to the HaRTC protocol by SIHB Traditional Health Professionals, who will provide ongoing consultation as needed.

Procedures

Screening, information and recruitment. Flyers and brochure will be posted on Facebook and at SIHB and other service providers to Indigenous and Native people. Potential participants will contact study staff via phone or email. Research staff will screen participants to see if they fulfill study criteria (i.e., identify as Native and/or Indigenous, urban-dwelling and not on Tribal/Reservation land, >21 years old, ≥4 on AUDIT-C, technologically literate for use of video conferencing/text). If so, research staff will hold online informational sessions (lasting approximately 20 minutes) and baseline assessments with interested parties. During informational sessions, research staff will explain the study procedures, study participants' rights and informed consent materials. The UBACC will be administered to assess capacity to provide informed consent. If they agree to participate, written informed consent will be obtained, and participants will be scheduled for a baseline visit and will be mailed a video-conferencing enabled smartphone (as needed) and at-home urine testing strips (i.e., 300 ng/ml one-step urine dipcards) to facilitate subsequent data collection and, as relevant, participation in the intervention. (Note: Participants will not be financially responsible for the smartphone in the case of its loss or damage, but only one replacement will be made available.)

Baseline data collection sessions. At baseline sessions, which will last approximately 60 minutes, participants will be administered the baseline measures, which will be recorded by research staff directly into REDCap. Then, they will dip the EtG dipcard in a urine sample cup they produced prior to the session into the provided specimen cup and show the results to staff, who will record the results in the same REDCap database (this will be the urine collection protocol throughout the study). Updated tracking/contact information will be collected and entered into a separate REDCap database.

Randomization. Study group assignments will next be determined by permuted block randomization. After each participant completes the baseline assessment, the assessment interviewer will receive the participant assignment via REDCap and reveal the participant's group assignment. Those randomized to HaRTC will be told the time and place of the first Circle in the next scheduled cycle and will be asked in the REDCap randomization section (not as data collection but for internal use): Would you like a medicine bundle sent to you? (y/n) Those randomized to the control group will be scheduled for the midpoint assessment, which is completed by all participants.

Intervention conditions. HaRT-C participants will be scheduled for their first intervention session. (If this does not occur immediately following the assessment, participants must be scheduled within two weeks of the completion of their baseline assessment). Participants in the HaRTC group will be invited to attend 8, weekly, closed-group Circles. They will be provided with information and demonstrations in how to use Zoom. All participants will be assessed at baseline, midpoint (4 weeks), posttest (i.e., immediately after the course of 8 weekly HaRTC sessions or within same amount of time if in TAU group), and at 1-, 3-, and 6-month follow-ups.

Prior to their first HaRTC, participants will be mailed a medicine bundle for personal use during the Circles as requested. HaRTC interventions will be led via videoconferencing (i.e., HIPAA-compliant Zoom connection) by Circle Keepers identified and trained by our partners at SIHB who are Traditional Health Professionals or who are recognized in their community as a Native health practitioner. They and will be hired as independent contractors at WSU or they will be SIHB employees. They will regularly attend CAB meetings and will undergo the same CITI and research ethics and confidentiality training and paperwork that WSU/UW research staff undergo prior to working with participants.

We will deliver HaRTC in 8, weekly, closed-group sessions, according to the protocol collaboratively developed by SIHB Traditional Health Professionals and WSU/UW researchers (see Appendices). Although the circles have no official running length, they typically last approximately 2 hours each. Throughout the study period, both HaRTC and control participants

will continue to have access to SIHB's usual supportive services will continue to receive to services as usual at SIHB or wherever they receive services. No attempts will be made to limit participants' access to community and clinical services during the study. Research staff will refer participants back to their clinical providers at SIHB, a fully licensed provider of medical, dental, mental health and substance-use treatment, or wherever they seek care in case the clinical need arises. Research staff will inform SIHB staff in case of a medical or mental health emergency. We can also refer participants to their local urban Indian health organization (UIHO; https://www.ncuih.org/UIHOs_locations), national crisis/suicide hotlines or emergency medical services, as appropriate.

At each subsequent assessment, participants will connect with HaRTC staff using the Zoom app that is set up/they have set up on their smartphone devices. Prior to all appointments, reminder calls/texts/emails will be made to participants, and the assessment will be entered unto the participants' REDCap calendar (which is also downloaded on the participants smartphone). Although HaRT-C participants will not be monetarily compensated for time in treatment sessions they attend, they will be offered a $40 incentive for attending all HaRT-C assessment sessions to facilitate complete in-session data collection.

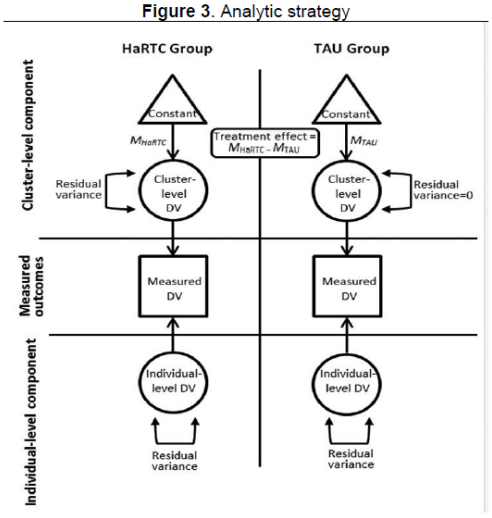
Control participants will follow the same schedule as HaRTC participants who were recruited during the same time period. Four weeks through each wave's HaRTC administration (and corresponding timepoint for delayed HaRTC participants) participants will complete a mid-point assessment. At the posttest and the 1-, 3- and 6-month follow-ups, all participants will undergo the same procedures as at previous assessments. They will be paid $40 for attending each assessment. Control group participants will be informed that they will have the opportunity to participate in non-study, no-cost HaRTC after their 6-mo follow-up.

Data Analysis Plan

Preliminary Data Analysis. Project Leads and members of the Research Methods Core of NCARE will conduct analyses for Phase 3. We will use descriptive statistics and plots to examine all study variables for missing values, outliers, and compliance with distributional assumptions for planned analyses. Next, we will compare study completers and non-completers on drinking and sociodemographic variables to detect potential patterns in attrition and missing data. As necessary, we will conduct analyses to determine whether missing data can be considered "ignorable." Research Methods Core staff will work with Project Leads to determine the most appropriate methods for addressing informative missing data. We will

then use direct maximum likelihood estimation for our structural models. Finally, we will examine baseline data to detect possible group differences on the primary outcome variables. As necessary, we will control for baseline group differences by using covariates in the primary outcome analyses.

Figure 3. Analytic strategy



Multilevel structural equation models will test partially nested group differences in changes in alcohol and QoL outcomes. Covariates were excluded from the figure to simplify presentation but will be entered as individual-level predictors. Circles are latent representations of dependent variables; squares represent measured dependent variables; triangles represent constants used to generate cluster-level latent variable means. DV = dependent or outcome variables; *M* = mean. (Adapted from Sterba et al.[121])

Accounting for the Partially Nested Design. Participants who are in the HaRTC group but not the control group will be clustered or nested within Circles (cluster level). We expect correlations among the measured outcomes of HaRTC participants who attend the same Circles. Such correlations would violate the assumptions of independence required for appropriate estimation of standard error in some statistical tests. Appropriate data analytic strategies are thus needed to accommodate correlations among participants in the HaRTC group. Multilevel structural equation modeling is one strategy that can account for non-independence in one arm and model effects at different levels of data organization

Analyses for RTC. A series of multilevel structural equation models will be fitted using Mplus 7.4127 to test the hypothesis that, compared to control participants, HaRTC participants will show significant improvements across outcomes over the short term (baseline to post-test) and longer term (baseline to 3- and 6-month follow-ups). Primary outcomes will include difference scores for alcohol (peak alcohol quantity, drinking frequency, alcohol-related harm, EtG, and QoL (general and HRQoL) outcomes.

Analyses for Secondary Data. Economic analyses will follow well-established guidelines. led by Robert Rosenman, PhD, who is leading economic analyses for NCARE. The measures listed in the cost analysis section above will be used for these analyses. Next, a cost-benefit analysis will estimate the downstream savings and net benefit of HaRTC relative to control. This analysis will provide a measure of “true cost” to the payer of healthcare services for the observed time frame. Cost-effectiveness will be summarized by using the incremental cost-effectiveness ratio (ICER), which is the incremental cost divided by the incremental effect of HaRTC relative to control. We will calculate ICERs with 2 types of effects. First, we will calculate

the cost per QALY, which accounts for both the duration of a particular health state and the associated HRQoL. We will also calculate an ICER with the more field-specific and clinically meaningful effect of per-point reduction in alcohol problems as measured by the SIP. Analyses will be conducted from the perspectives of the Figure 3. The payer perspective is important because payers, such as health insurance companies, sustain treatment programs. The societal perspective is important because it also incorporates indirect costs (e.g., school and workplace productivity, criminal justice outcomes, patient travel time) that are relevant to patients and the general public.

Similar to the analyses for Specific Aim 2, we will use multilevel structural equation modeling to account for the partially nested design in predicting mean values for each resource category, per-point reductions in alcohol problems, and HRQoL preference weights at each time point. QALYs gained in the HaRTC group will be estimated by using the area under the curve methodology. The method of recycled predictions will be used to obtain the final predicted mean values for each study arm and resource, which will then be summed and tested from both the payer and societal perspectives. To account for sampling uncertainty in point estimates, the p values, standard errors, and confidence intervals for ICERs will be estimated by using nonparametric bootstrapping. Parameters obtained from bootstrapping will be used to estimate acceptability curves, which estimate the probability that HaRTC is a good value for different willingness-to-pay thresholds (e.g. cost per QALY). Sensitivity analyses will be conducted to assess precision in assumptions and parameter estimates.

Secondary Mediation Analyses. If our primary analyses indicate a statistically significant HaRTC effect, we will conduct secondary analyses of AI/AN enculturation as a potential mechanism underlying improvements in alcohol and QoL outcomes. Such mediation analyses, however, require very large sample sizes to achieve the necessary power to detect statistically significant relationships.

Because it is impracticable to achieve an adequate sample size for mediation analyses in the proposed project, we will test mediation as an exploratory research question. In addition to their ability to accommodate data clustering at various levels, multilevel structural equation models allow for unbiased estimates of both individual- and cluster-level indirect effects. This makes multilevel structural equation modeling ideal for testing mediation. In our mediation model, intervention group (HaRTC versus control) will serve as a cluster-level predictor of outcome, and baseline-to-posttest change in AI/AN enculturation will serve as the mediator. To test mediation, we will follow procedures outlined by Lachowitz et al., which are essentially an adaptation of the product of coefficients method. First, we will constrain the cluster-level effect of

the mediator on the outcome to be equal across HaRTC and control groups. Second, we will multiply the difference between the mediator means for the HaRTC and control groups by the effect of the mediator on the outcome. This parameter will provide an indirect, cluster-level effect for HaRTC on outcomes as mediated by change in AI/AN enculturation.