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Mixed-methods trial of a phosphatidylethanol-based contingency management intervention to initiate and maintain alcohol abstinence in formerly homeless adults with alcohol use disorders

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ABSTRACT

Background: Contingency management (CM) is an intervention where incentives are provided in exchange for biochemically confirmed alcohol abstinence. CM is effective at initiating alcohol abstinence, but it is less effective at maintaining long-term abstinence. Phosphatidylethanol (PEth), collected via a finger-stick, can detect alcohol use for 14–28 days. PEth allows for the development of a CM model that includes increasingly less frequent monitoring of abstinence to assist high risk groups, such as formerly homeless individuals, maintain long-term abstinence.

Aims: Investigate whether PEth-based CM intervention targeting alcohol abstinence in formerly homeless, currently housed individuals with alcohol use disorders is: (1) acceptable and feasible for housing program tenants and personnel; and is associated with increased (2) alcohol abstinence and (3) housing tenure.

Methods: Acceptability and feasibility will be assessed using a QUAL + quant mixed-methods design using qualitative interviews and quantitative measures of satisfaction and attrition. Effectiveness will be evaluated through a randomized pilot trial of 50 study participants who will receive 6 months of either treatment as usual (TAU) including incentives (e.g., gift cards) for providing blood samples (Control Condition) or TAU and incentives for negative PEth results (PEth-CM Condition). Outcomes will be assessed during the intervention and at a three-month follow-up visit. The trial will be conducted via telehealth as a result of COVID-19.

Discussion: This protocol seeks to utilize a novel alcohol biomarker to evaluate the acceptability, feasibility, and initial effectiveness of a CM model that encourages long-term abstinence in a high-risk group.

1. Introduction

Nearly 40% of people experiencing homelessness have a diagnosable alcohol use disorder (AUD) [1]. When individuals experiencing homelessness find housing, AUD is associated with decreased housing tenure, impaired health, increased cost in medical treatment, and employment problems [2–10]. Once housed, formerly homeless individuals face barriers to obtaining treatment, including stigma, poor insurance coverage, lack of transportation to treatment appointments, and lack of knowledge of treatment options [11–14]. Most AUD treatments provided in supported housing programs prioritize addressing barriers to access (e.g., intensive case management) or providing housing (e.g., housing first) rather than offering evidence-based interventions [15–19].

Contingency management (CM) is an intervention for AUD in which individuals receive tangible incentives in exchange for biochemical verification of alcohol abstinence [20]. Typically, CM models for alcohol abstinence rely on ethyl glucuronide urine tests, with a detection limit of 2–5 days [21–24], gathered twice weekly to verify alcohol abstinence. Most CM interventions are designed to support patients in estab-

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lishing abstinence during outpatient treatments that last approximately three months [25,26]. While CM is an effective strategy for initiating abstinence early in treatment, the effects of CM after treatment is less clear [21,26–30]. There is a need to modify CM to help people maintain long-term abstinence, especially for groups at high-risk of relapse.

Phosphatidylethanol (PEth) is a metabolite of ethanol and a direct biomarker that is detectable in blood for up to 28 days after alcohol use and collected using a finger-stick method [31–36]. There are no reports of false positive tests when a cutoff of 20 ng/mL of PEth 16:0/18:1 is employed [37–40]. The use of PEth allows the assessment of abstinence and the delivery of CM to be conducted as infrequently as once a month, resulting in a feasible model to help individuals with AUDs initiate and then maintain abstinence. While once a month PEth testing may not detect all alcohol use, it is likely to detect clinically significant alcohol consumption should it occur [37,40,41]. In a within-subject design study, weekly PEth samples were obtained from five participants over a 10-week period [42]. Findings established sample collection was feasible and participants were 2.3 times more likely to submit negative PEth samples when incentives were contingent on PEth verified abstinence compared to incentives being received regardless of PEth results [42].

The current protocol is designed to appraise whether a PEth-based CM intervention helps residents with an AUD in supported housing initiate and maintain alcohol abstinence over a nine-month period. The aims are to evaluate the feasibility and acceptability of the PEth-based CM intervention in supported housing programs using a QUAL + quant design and determine group differences in alcohol abstinence, assessed by the PEth biomarker, and housing tenure. Additionally, in light of COVID-19 and the movement of behavioral healthcare to telehealth, the protocol was modified to conduct the study via telehealth.

2. PEth-based CM acceptability and feasibility methods

2.1. Qualitative design

To appraise acceptability and feasibility of the intervention in a housing program, qualitative interviews will be performed via videoconferencing with:

a) 25 PEth-CM Condition participants (Condition described in 'PEth-Based CM Effectiveness Methods'); and
b) 25 supported housing personnel, 20 housing staff and 5 administrators.

While the PEth-CM participants semi-structured interviews will assess the participants' acceptability of the intervention, the qualitative interviews with supported housing personnel will be informed by the Theoretical Domains Framework (TDF) [43,44], an intervention implementation framework, where the 14 domains will appraise the personnel participants' behaviors, perceptions, and knowledge around the feasibility of the intervention in a supported housing program.

2.2. Qualitative procedures

2.2.1. PEth-CM condition interviews

Participants randomized to the PEth-CM condition will take part in 3 qualitative interviews at their week 4, 26, and 38 visits. These semi-structured interviews will be conducted via phone or videoconferencing and will last approximately 30 minutes. Their beliefs will be evaluated around the acceptability of the intervention (e.g., acceptability of the finger-sticks) and their perceptions of the intervention being offered in their residence and via telehealth. Due to the repetitive schedule of the interviews, research staff will be able to observe how their beliefs evolve and to delve deeper with varying cogitative questions. As these interviews coincide with the quantitative monthly visits (described below), participants will receive $20 in e-gift cards for completion of the visit.

2.2.2. Supported housing personnel interviews

Upon completion of the PEth-based CM effectiveness portion of the study, 25 supported housing personnel, 20 housing staff and 5 administrators, will be recruited to evaluate the feasibility of the CM intervention in a supported housing program. These semi-structured interviews will be informed by the TDF to identify their beliefs and perceptions around the intervention as well as the potential administration of the intervention by housing personnel. These interviews will last approximately an hour and personnel participants will be compensated with $30 in e-gift cards.

2.3. Mixed-methods assessments

2.3.1. Mixed-methods acceptability and feasibility

Acceptability of the intervention will be appraised using quantitative data assessed by the Client Satisfaction Questionniare-8 (CSQ-8) [45], administered at the quantitative monthly visits, and attrition rates throughout the study. PEth-CM Condition participants will engage in qualitative interviews at 3 timepoints in the study. These interviews will be transcribed and coded as described in the 'Planned Analyses' section to allow for a thematic analysis in comparison to the quantitative measures. These three measures evaluated alongside each other will allow research staff to assess whether PEth-based CM is an acceptable means to initiate and maintain prolonged abstinence in formerly homeless individuals living in supported housing programs.

To assess the feasibility of implementing a PEth-based CM protocol in supported housing programs, semi-structured qualitative interviews will be conducted with housing personnel to identify possible barriers and facilitators for implementing this intervention in a supported housing program. These interviews will be informed by the 14 TDF domains (See Table 1), where beliefs and behaviors are identified as well as barriers and facilitators [43,44] in implementing this intervention in similar housing programs. The TDF discerns potential difficulties with implementation of the intervention and informs the design for future implementation [43,44].

3. PEth-based CM Effectiveness Methods

3.1. Quantitative design

Effectiveness of the CM intervention will be discerned by conducting a pilot randomized controlled trial of 50 formerly homeless adults with an AUD residing in supported housing programs located in Spokane, Washington. Participants will be randomized to one of 2 treatments for a six-month period:

a) Control Condition: participants receive treatment as usual (TAU) alongside incentives for submitting blood samples irrespective of PEth results; or
b) PEth-CM Condition: participants receive TAU and incentives for PEth results consistent with alcohol abstinence (e.g., decreasing until levels reach <20 ng/mL and maintenance of levels <20 ng/mL).

A follow-up assessment will be conducted three months after completion of the treatment period. Fig. 1 describes the overall study design. All study protocols were reviewed and approved by Washington State University (WSU) Institutional Review Board (IRB).

Table 1
Theoretical Domain Framework[a,b] for implementation of an intervention.

Domain	Definition[c]	Potential Qualitative Question
Knowledge	An awareness of an issue	Are you aware of any evidence-based practices to address alcohol use?
Skills	An ability or proficiency acquired through practice	Have you had any training on evidence-based treatments for initiating abstinence from alcohol with individuals? If so, could you please describe.
Social and professional role and identity	A set of behaviors of an individual in a social or work setting	What is your role with Catholic Charities? How do you view your role (or someone who holds the same role) in addressing alcohol use with tenants?
Beliefs about capabilities	Views about an ability, talent, or facility that can put to constructive use	What would you need to implement this intervention in your housing program?
Optimism	The confidence in best case outcomes or desired goals reached	Do you believe this intervention will help tenants? Why or why not?
Beliefs about consequence	Realistic views about outcomes in a given situation	Do you believe this is an intervention that would be of interest to tenants? Could you please explain why?
Reinforcement	Increasing the probability of a response by modifying behavior or act in a certain way	Do you believe the benefit of the intervention outweighs possible barriers? Please explain.
Intentions	A conscious decision to perform a behavior or act in a certain way	How important is it to you to have an evidence-based intervention for alcohol use in your housing program? Please explain.
Motivation and goals	Outcomes or end states that an individual wants to achieve	What steps would need to be addressed to implement this intervention in the residences?
Memory, attending and decision processes	The ability to retain information, focus on select aspects and choose between two or more alternatives	In what instance would you recommend an individual to this intervention over another?
Environment context and resources	Person's environment that discourages or encourages the development of skills, abilities, and adaptive behavior	What do you anticipate being the barriers and facilitators in implementing this intervention in your housing program?
Social influences	Interpersonal processes that can influence an individual's thoughts, feeling, or behaviors	Do you believe the administrative level of your housing program would be supportive of implementing this intervention in the residences? Please explain.
Emotion	A reaction pattern, involving behavioral and physiological elements, allowing the individual to deal with a matter or event	If it were determined that your role would be responsible for implementing this intervention, do you believe it would provoke more stress, burn-out or other emotions than your current day-to-day responsibilities?
Behavioral regulation	Anything aimed at managing or changing observed or measured actions	What procedures or ways of implementing this intervention that would encourage you to use it for alcohol use with your tenants?

[a] Cane et al., 2012
[b] Atkins et al., 2017
[c] All definitions are based on definitions from the American Psychological Associations Dictionary of Psychology [46].

3.2. Quantitative procedures

3.2.1. Participant eligibility

Inclusion criteria are: 1) age 18–65 years old; 2) 1 or more days of having 4/5 (females/males) or more drinks in the last 30 days; 3) PEth levels ≥20 ng/mL; 4) diagnosis of AUD by the DSM-5 [47] as assessed by the Structured Clinical Interview for DSM-5 (SCID-5) [48]; 5) currently housed at the supported housing program; and 6) previous homelessness or unstable housing for >30 days. Exclusion criteria include: 1) current diagnosis of DSM-5 severe substance use disorder (other than AUD, tobacco, or cannabis); 2) inability to provide informed consent based on the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) [49]; 3) alcohol withdrawal-related seizure or hospitalization in the previous 12 months; 4) psychiatrically or medically unsafe to participate in study, as assessed by the Principal Investigator (PI); or 5) currently enrolled in another CM study.

3.2.2. Randomization procedures

After completing a baseline visit and verifying eligibility (i.e., PEth ≥20 ng/mL indicating alcohol use along with other inclusion criteria), participants will be randomized to the non-contingent Control Condition or the PEth-CM Condition using permuted block randomization. Participants will be stratified for randomization by sex and baseline levels of urine ethyl glucuronide (uEtG) (<500 ng/mL and ≥500 ng/mL), as ≥500 ng/mL is an indication of heavy drinking over the previous two days and a predictor of poor CM outcomes [50].

3.3. Interventions

3.3.1. Non-contingent control condition

Participants will receive TAU as provided by the housing program, which include social services and access to mental health and substance use providers in the community that are offered onsite or at neighboring community clinics. Additionally, participants will receive an incentive for submitting blood samples and completing all measures described below. The Control Condition schedule approximates the monitoring and reinforcement of individuals continuously abstinent from alcohol in the PEth-CM Condition: weekly visits for a month, every other week visits for a month, then monthly visits for 4 months (See Fig. 1). Consistent with other CM studies, the level of reinforcement received by the Control Condition matches the average value of incentives received by the PEth-CM Condition during the previous month of the study but no less than $20 per sample submitted, with an additional $10 for completion of the visit [21,27].

3.3.2. PEth-CM condition

Participants will receive TAU, a $10 attendance incentive for submitting a blood sample and completing the visit as well as PEth-based incentives contingent on PEth results consistent with alcohol abstinence (described in more detail below). The PEth-based incentive for an abstinent test result will be at least $20 per sample (an escalating schedule of reinforcement will be used, see Table 2). The PEth CM Condition will include two phases, one focused on establishing abstinence (weekly visits for at least a month) and the second focused on maintaining abstinence (every other week for a month, followed by monthly visits for 4 months). The escalating schedule of reinforcement will be based on consecutive decreases in PEth levels (in Phase 1) or negative PEth results (<20 ng/mL in Phase 2) (See Table 2). For each consecutive visit with an abstinence result confirmed by PEth, an additional $5 will be added to the previous week's PEth-based incentive (up to $90 each week). Individuals who submit negative PEth samples (or decreasing PEth levels in Phase 1) each week can obtain a total of $2,075 over the 6-month study. However, based on previous CM studies, the actual total incentives pay-out is projected to be closer to ~$1,037 due to missed visits or positive results [42].

Phase 1. Finger-stick blood samples will be collected once a week until participants achieve a PEth level <20 ng/mL, which is consistent with long-term abstinence (approximately 4 weeks) [42]. Abstinence will be defined as a week-to-week decrease in PEth 16:0/18:1. Participants will remain in Phase 1 for at least 4 weeks. Participants will then move to Phase 2 once they attain a PEth level <20 ng/mL. Those who do not attain a PEth <20 ng/mL in 4 weeks will continue in Phase 1 until it has been attained.

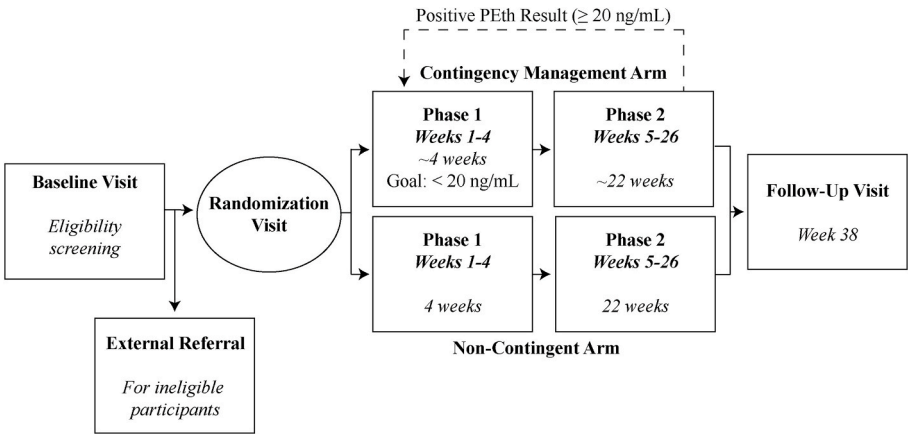

Fig. 1. Overview of study procedures for the two conditions.

Table 2
Maximum CM payout for continuously abstinent participants (Amounts do not include $10 visit attendance incentive).

Week	Amount Earned	Payment Received	Week	Amount Earned	Payment Received
1	$20	$20	14	$85	
2	$25	$25	15	$90	
3	$30	$30	16	$90	$345
4	$35	$35	17	$90	
5	$40		18	$90	
6	$45	$85	19	$90	
7	$50		20	$90	$360
8	$55	$105	21	$90	
9	$60		22	$90	
10	$65		23	$90	
11	$70		24	$90	$360
12	$75	$270	25	$90	
13	$80		26	$90	$180

Phase 2. Blood samples for PEth analysis will be collected and incentives provided every two weeks for a month (weeks 6 & 8) then once every four weeks (weeks 12, 16, 20, 24) for 4 months with a final treatment visit at week 26. PEth-based incentives will only be awarded when participants submit samples that are consistent with long-term abstinence (PEth <20 ng/mL). If a participant submits a sample with PEth levels ≥ 20 ng/mL, indicating alcohol use, they will re-enter and remain in Phase 1 until PEth returns to <20 ng/mL (See Fig. 1). Therefore, each participant's CM schedule will be tailored to their ability to maintain long-term abstinence; however, everyone will receive 26 weeks of PEth-CM treatment in total.

3.3.3. Data collection

In light of COVID-19, recruitment and all participant visits will be accomplished via telehealth, including both videoconferencing and phone. For participant recruitment, flyers, brochures, and contact forms with study contact information will be made readily available at the participating housing programs. Any inquiries regarding the study will be fielded by contacting the study email, phone, or mailed in contact forms. Screening of potential participants will occur over the phone rather than in-person. Participants eligible after the initial screening will attend and receive $30 in gift cards for completing a two-hour baseline visit. At the baseline visit, participants will attend the visit by means of HIPAA compliant videoconferencing platform, Zoom for Healthcare, and provide informed consent via REDCap's electronic-consenting platform. Informed consent is appraised by the University of California, San Diego Brief Assessment of Capacity to Consent [51] and/or MacCAT [49]. Additionally, the baseline visit includes a finger-stick blood sample, urine sample, and self-report data (see below for details). Upon completion of baseline self-report measures, participants will be trained to collect their own samples. For blood collection, participants will watch a video demonstration along with a question and answer session. During the blood sample collection at all visits, participants will collect their blood sample while study staff observe and provide coaching.

Individuals that are eligible after baseline will attend a randomization visit where they will provide a blood sample, urine sample, and self-reported alcohol consumption data, as well as be randomized and informed of their treatment condition. At each subsequent visit, participants will provide blood and urine samples, self-report data on alcohol and substance use, and information on housing tenure. Other measures assessing alcohol-associated harms will be collected at monthly visits (weeks 4, 8, 12, 16, 20, 26 and 38, see Table 3). Participants will receive $20 in gift cards for completing these monthly visits. All participants will return for a follow-up visit 12 weeks after their last treatment visit (week 38 visit). This visit will last for approximately an hour and include finger-stick blood sample, urine sample, and self-report data similar to the baseline visit. Participants will be compensated with $20 in gift cards for this final visit.

Table 3
Measure collection schedule.

Randomized Participant Assessments	Baseline	Each Study Visit	Week 4, 8, 12, 16, 20, 26, 38 Interview
Eligibility Criteria	✓		
Primary Acceptability Outcomes			
Attrition		✓	
Client Satisfaction: CSQ-8			✓
Participant Qualitative Interviews			Weeks 4, 26, 38
Aim 2 Outcomes			
PEth Blood Test	✓	✓	
Self-Reported Drinking: A-TLFB	✓	✓	
Urine Ethyl Glucuronide	✓	✓	
Aim 3 Outcomes			
Housing Status: Residential TLFB	✓		✓
Drug Use Severity: ASI-Lite	✓		✓
Psychiatric Symptoms: NIH Toolbox	✓		✓
Physical Health: SF-12	✓		✓
Healthcare/Jail Utilization: NSRF	✓		✓
Adverse Events	✓	✓	✓
Housing Personnel Assessment		**Upon Study Completion**	
Qualitative Interview		✓	

To ensure that samples are not falsified during visits, spot cards and UA cups will be mailed to participants with their ID, visit number, and date of collection specified on each. Participants will videoconference with research staff to allow observation of the blood specimen collection to verify results; the visit will then be finished via phone or videoconference. Additionally, urine samples will continue to be collected, although results cannot be verified. Participants will send an electronic picture of the spot card to the study phone number or email and then drop off both samples at their designated drop box.

Upon receipt, research staff will package the cards into one shipment and send to University of Texas Health San Antonio (UTHSA) for analysis. At this time, Control Condition participants will be administered their incentive via electronic gift cards for completion of visit and collection of their sample. For CM participants, if PEth results indicate abstinence (decreasing in Phase 1 or <20 ng/mL in Phase 2), PEth-based incentives will be administered in the form of electronic gift cards; otherwise, CM participants will simply receive their attendance incentive.

3.4. Quantitative assessments

3.4.1. Alcohol and drug biomarkers

Blood and urine samples will be collected at each visit. Blood will be drawn via a finger-stick method using a High Tech Lab Strefa Medlance Safety Lancet Extra (21 G 2.4 mm) and transferred to a Protein Saving Spot Card (HemaXis DB 10 Device). At least two of the four spots on the card will be filled with approximately 50 μL of blood [32,38]. Spot cards will dry overnight at room temperature and then be stored in a cold, dark drawer until shipped to UTHSA [52]. For shipment, each spot card will be placed in individual biohazard bags with a desiccant pack to ensure no moisture contaminates the sample. Upon arrival at the UTHSA lab, samples will be analyzed for 3 PEth homologues: 1-palmitoyl-2-oleoyl-phosphatidylethanol (PEth 16:0/18:1), 1-palmitoyl-2-linoleoyl-phosphatidylethanol (PEth 16:0/18:2), and 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphoethol (PEth 16:0/20:4). Analysis of the blood samples will be conducted using high-performance liquid chromatography (HPLC) and mass spectroscopic detection [32]. Solvents and reagents used for the analysis will be analytical grade and purchased from Thermo Fisher or Sigma Chemical (St. Louis).

To extract PEth samples from the spot card, four 6 mm punches will be collected from dried blood spots on the card. These punches are then mixed with isopropanol and hexane in succession. Once thoroughly mixed, the organic material is dried to residue under a gentle stream of nitrogen at room temperature. The residue is dissolved in HPLC mobile phase for injection into mass spectrometer. The ratios of the AUC of the peaks of PEth 16:0/18:1, 16:0/18:2, 16:0/20:4 to their corresponding deuterated internal standard are compared to a linear regression of the ratios of calibrators to quantify PEth homolog concentrations in each sample. In Phase 1, abstinence is determined by the PEth 16:0/18:1 biomarker decreasing from the previous, or “baseline”, PEth level. In Phase 2, PEth 16:0/18:1 levels <20 ng/mL are interpreted as recent abstinence.

At each visit, a urine sample will be collected and uEtG levels assessed as a secondary biomarker. The level of uEtG will be quantified using the Thermo Fisher Scientific Indiko Bench Top Analyzer and all reagents and solutions purchased through Thermo Fisher Scientific. uEtG levels of <100 ng/mL indicates abstinence, while ≥ 100 ng/mL indicates recent alcohol use and levels ≥ 500 ng/mL indicates recent heavy alcohol use [50]. Illicit drug use will also be assessed via urine using UScreen Drug Test Cup; a 5 panel instant drug test assessing cannabis (tetrahydrocannabinol ≥ 50 ng/mL), opioids (morphine ≥ 2000 ng/mL), amphetamines (d-amphetamine ≥ 1000 ng/mL), methamphetamines (D(+)-methamphetamine ≥ 1000 ng/mL), and cocaine (benzoylecgonine ≥ 300 ng/mL) via the EZ-split immunoassay.

3.4.2. Self-report of alcohol use

Self-reported alcohol use will be assessed at each visit using the Alcohol Timeline Follow Back [53]. The frequency and the amount of alcohol used is recorded for each day since the previous visit. At each monthly visit, the Addiction Severity Index Lite (ASI-Lite) will be administered [54–56]. The ASI-Lite assesses the impact of the participant's recent alcohol use as well as alcohol use on medical, psychiatric, legal, and family dynamics.

3.5. Additional outcome measures

3.5.1. Alcohol-related health and harms

Measures around health and harms due to impairment include the Short Form Health Survey-12 [57] and Non-Study Services Resource [58–61] forms. Physical health and alcohol-related medical and criminal justice utilization are reported, respectively.

3.5.2. Housing tenure

An individual's housing history will be assessed using the Homeless History Timeline (developed in the RAND study) at their baseline visit. At each monthly visit, housing status will be documented using the Housing Timeline Follow Back's 34 distinct categories (See Table 4) [16].

3.5.3. Other variables

At each monthly visit the NIH Toolbox Emotion battery is performed to assess the participant's stress, emotions (i.e., fear, sadness), relationships, and wellbeing [62]. An individual's nicotine use is measured by a Timeline Follow Back [63] and the Fagerström Test of Nicotine Dependence to assess the presence of nicotine dependence and severity [64].

Measures administered only at baseline visits include the SCID-5 [48] and the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) [65]. The SCID-5 assesses the participant for a current AUD and substance use disorder [48], to ensure eligibility for the study, while the SOCRATES assess the individual's motivation and eagerness to change alcohol use habits [65].

Table 4
Housing timeline follow back.

Housing Categories			
1	Public Space, e.g. All-night theater or bus station	18	Parent or Guardian's Apartment or House (Long-Term)
2	Light Rail or Bus	19	Other Family Member's Apartment or House (Temporary)
3	Abandoned Building	20	Other Family Member's Apartment or House (Long-Term)
4	Car or Other Private Vehicle	21	Someone Else's Apartment or House (Temporary)
5	On the Street or in Another Outdoor Place	22	Someone Else's Apartment or House (Long-Term)
6	Emergency Shelter	23	Boarding House or Board-and-Care
7	Hotel or Motel	24	Transitional Housing Program (Short-Term with Link to Long-Term)
8	Own Single Room Occupancy (SRO) with No Services	25	Transitional Housing Program (Short-Term without Link to Long-Term)
9	Someone else's SRO with No Services	26	Transitional Housing Program (Long-Term)
10	Supportive SRO (Services On-Site)	27	Group Home
11	Drop-In Center	28	Long-Term Alcohol/Drug-Free Facility
12	Safe Haven (Low Demand Facility, Reception Center)	29	Hospital (Medical Only)
13	Detox Facility	30	Nursing Home
14	Crisis Housing	31	Treatment or Recovery Program
15	Intermediate Care Facility	32	Jail or Prison
16	Own Apartment or House	33	Corrections Halfway House
17	Parent or Guardian's Apartment or House (Temporary)	34	Psychiatric Hospital or Facility (Includes any Inpatient Psychiatric Stays)

3.5.4. Reporting adverse events

Any vocalized adverse events are assessed at each visit and discerned whether a serious adverse event has occurred. The PI will determine whether the adverse events are associated with the study protocol. If adverse events are determined to be associated with the study protocol, modifications will be made to ensure the safety of the participants and future studies. In the case that modifications cannot be implemented, the study will be dismissed. If a potential serious adverse event takes place during the study, all procedures and recruitment will cease until an investigation is conducted by the PI and Co-Investigators. The investigation determines whether the event is classified as a serious adverse event using the standard US Food and Drug Administration guidelines. Any events determined to be a serious adverse event will be reported immediately to the following organizations: IRB, which will function as the study's Data Safety Monitoring Board (DSMB), partnered agency, and the NIH. All non-serious adverse events will be conveyed to the IRB in an annual report during the continuing review as well as the program official.

4. Planned data analyses

4.1. Preliminary analyses

Statistical analysis and results will be reported in accordance to the CONSORT guideline [66]. Baseline data will be used to determine whether any covariates need to be considered as confounders for the primary analyses. To do so, baseline data will be analyzed using parametric tests or nonparametric tests, depending on the nature of the variables. For categorical variables, chi-squared test will be used. For continuous variables, analysis of variance (ANOVA) for parametric test and Mann Whitney *U* test for non-parametric will be used. Multiple-testing adjustments (e.g., Bonferroni correction) will be performed as needed. In addition, the impact of sex will be assessed on all outcomes, as alcohol use severity and housing tenure might vary by sex. The alpha threshold for statistical significance will be 0.05.

4.2. Participant acceptability

Attrition will be measured as a yes/no variable when the participant has not contacted study staff for 4 consecutive weeks. From previous studies, attrition rates ≤30% will be deemed acceptable [21]. A Cox proportional hazards model to determine whether there are predictors independently associated with time-to attrition. These potential predictors include demographic variables (e.g., sex) and severity of alcohol-problems. Additionally, the participant satisfaction survey's (CSQ-8) raw mean differences after dichotomizing the scale will be assessed between the two conditions using linear mixed regressions. An individual score of 24, averaging 3 (satisfied) on the 8 items, indicating satisfaction with the intervention.

4.3. Qualitative data analysis

Interviews will be audio recorded, transcribed, and reviewed for accuracy. These interviews and their de-identified transcriptions will be stored in a HIPAA compliant database. The de-identified transcripts will be uploaded to ATLAS.ti software, where qualitative specialists will conduct coding and organize themes across interviews [67]. The deductive analytical strategy uses existing theory to inform and structure the coding process. This allows for the validation, expansion, and refutation of frameworks or theories [68]. The interviews from CM participants and housing personnel will incorporate concepts from previous CM studies as well as those unique to PEth CM (e.g., acceptability of finger-sticks) and the housing program in order to develop and operationalize the coding scheme. The TDF will be used to develop and derive key themes and codes from the interviews with housing personnel. Two qualitative specialists will independently read each transcript and note text corresponding to initial codes and memos describing the codes application to the text. They will then meet weekly to discuss their application of codes, develop codes not currently capturing key concepts, and identify patterns and themes until a final code book is developed. To protect from biases, an audit trail will be kept of the analytical discussions, further evaluation of cases that could not be coded with initial thematic schema, and the development of additional codes not present in the initial key [69]. The data will be coded using the final code book and reports will be generated in ATLAS.ti to identify patterns, emerging themes, and barriers and facilitators to implementation of CM in supported housing programs.

4.4. Mixed-method integration

The thematic matrix will be developed from the PEth-CM participants interviews. This will be integrated in the analysis of acceptability through the satisfaction and attrition data with the participants [70,71]. This matrix will enable direct comparison between the themes derived from the interviews with the participants' satisfaction and attrition measures. This will allow the research team to note themes that may help deduce the participants' satisfaction with the intervention and reasons for attrition. Additionally, this matrix will allow for comparison with barriers and facilitators identified in personnel interviews, further developing and shaping future implementation design.

4.5. Effects of CM on alcohol use and housing tenure

The primary alcohol outcome is abstinence as assessed by the PEth biomarker. With an anticipated attrition rate of ≤30% [21], it will be assumed that the data will be missing at random (MAR). To account for the missingness, a mixed-effects regression models will be used in estimating the association between contingency management and alcohol abstinence. An effect of time and condition-by-time interaction will be added in the mixed-effects regression model to determine if the outcomes vary over time and differentially over time by condition. In addition, an alternative analysis using multiple imputation will be conducted to estimate the association using generalized linear model with generalized estimating equations (GEE). Other cross-sectional outcomes, such as longest duration of abstinence, housing tenure, and total number of alcohol negative PEth samples submitted, will be analyzed using logistic regression (i.e., binary outcomes) and Poisson regression (i.e., count data). These outcomes will be assessed between the two conditions. Group comparisons of other aims' outcomes will be assessed in a similar manner.

4.6. Missing data

Extensive steps will be taken to prevent missing data. Although our mixed-effects regression model approach handles incomplete data, we will explore other alternatives in handling missing data. Multiple imputation and other sensitivity analyses, including "missing not at random" approaches, will be used to account for any possible missing data [27,72–74].

4.7. Power analysis

With a sample size of n = 50, the statistical power calculation will primarily aim to detect differences between PEth-assessed alcohol abstinence across the 6 months of treatment and the follow-up visit. The aforementioned missing data techniques will assist in recapturing some power lost due to attrition. Power analyses will use alpha threshold for statistical significance of 0.05. For the primary outcomes of binary alcohol use measured via PEth, there will be at least 82% power to detect a 12% difference between the two conditions (odds ratio, OR = 1.70)

[42]. It is likely the group will change at different rates. When examining the group-by-time interaction, there will be at least 80% power to detect an OR of 1.35, or a 7% group difference. Thus, the detectable effect size will be much smaller than the 30% difference in abstinence observed in the previous within-subjects design study [42]. Based on these estimates, there will be sufficient power to detect differences in alcohol-related outcomes. For non-alcohol-related outcomes, potential group differences will be compared. While the group differences will be assessed, the power analysis is primarily aimed at inferential analysis of the primary outcomes.

5. Discussion

CM is associated with the initiation of alcohol reduction in adults with an AUD. The PEth biomarker, where samples for incentives are collected monthly once abstinence has been obtained, is a promising strategy to reduce alcohol use and prolong housing tenure in this high-risk population. Moreover, PEth-CM as an intervention is more feasible for supported housing programs as fewer visits are required for monitoring abstinence and delivering incentives. Furthermore, it could be implemented without additional staffing or licensed clinical providers. If results support the acceptability, feasibility, and initial effectiveness of the PEth-based CM intervention, it will allow housing programs to provide effective alcohol intervention thereby addressing important barriers to AUD treatment access, such as travel time and cost. This protocol is important because it 1) focuses on evaluating a CM model in a housing program, 2) using PEth as method to monitor abstinence to deliver a flexible model of CM, that supports initiating and maintaining abstinence, and 3) could lessen case manager burden if effective as a telehealth intervention where one clinician could deliver the intervention across multiple housing facilities.

The QUAL + quant design will allow us to identify reasons for attrition and treatment success which may inform future PEth-based CM studies and acceptability of PEth collection. Using the TDF, barriers and facilitators will be identified to potentially modify the PEth-based CM intervention for real world application in supported housing programs in addition to their beliefs of its effectiveness as an intervention via telehealth. With the PEth biomarker needing less frequent monitoring, the PEth-based CM intervention may be viewed as a more feasible behavioral intervention for maintaining long-term abstinence from alcohol. Furthermore, PEth-based CM may assist a population that previously has not been successful in maintaining long-term abstinence in other interventions. Results from this study will inform a larger hybrid effectiveness and implementation trial that will be sufficiently powered to evaluate the effectiveness of this intervention and assess factors that affect implementation across multiple housing programs.

Given the impact of COVID-19 related stay-at-home orders and the subsequent increase in the use of telehealth interventions to treat an AUD, our modified protocol will additionally allow us to evaluate a slightly adapted telehealth version of a PEth-based CM intervention.

While limitations will be explored further upon completion of this pilot study, some such limitations should be addressed. CM has repeatedly been determined to be an effective treatment in initiation of abstinence from substances [25,26]; however, federal policies on funds continue to limit the ability to implement CM in behavioral health organizations. Additionally, the incentives for continuously abstinent individuals are relatively high in this pilot study. This protocol contains a novel collection process that requires a delayed distribution of incentives of up to a week. As a result, the value of incentives is higher than a typical CM interventions to account for this delay. Further, the overall cost of the CM intervention is larger than a typical CM intervention as the intervention is six months in duration, rather than the typical three-month intervention. Many participants will have missing or submit alcohol-positive samples, leading to a per participant cost (approximately $1,000) that is much lower than the maximum potential cost of incentive (approximately $2,000) (i.e., someone who submits all alcohol-negative samples). If successful, we believe the costs of this CM intervention will be offset by cost savings associated with reductions in alcohol consumption, longer housing tenure, and other cost savings (e.g., lower utilization of acute or inpatient treatment). It is likely that the cost savings of preventing loss of housing alone is significant and an economic analysis in a subsequent study will determine the cost effectiveness of this novel PEth-based CM approach, as observed in previous studies which found CM to be cost effective [75–77]. Furthermore, reduced incentive amounts could be assessed in future trials to reduce overall cost burden once acceptability and feasibility of PEth-based CM interventions are established.

It is our hope that this novel approach to CM for AUDs, if determined to be acceptable and feasible, will provide a sustainable intervention which can be administered outside of a clinic-based setting. With less monitoring and an individualized, tailored schedule, PEth-based CM has the potential to increase access to an effective treatment for AUD.

Declaration of competing Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

The opinions and assertions expressed herein are those of the author (s) and do not necessarily reflect the official policy or position of the Uniformed Services University or the Department of Defense.

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