Title: Financial Incentives, Randomization with Stepped Treatment (FIRST) Trial

Last Yale IRB Approval Date: 3/10/2024

Yale IRB #: 2000020383

NCT #: NCT03089320

IRB Protocol and

Statistical Analysis Plan (p. 30, sec. 9)

YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: **F**inancial **I**ncentives, **R**andomization with **S**tepped **T**reatment (**FIRST)** trial			
Principal Investigator: David Fiellin, MD		**Yale Academic Appointment:** Professor	
Department: General Medicine			
Campus Address: 367 Cedar Street, Suite 406			
Campus Phone: 737-3347	**Fax:** 737-3306	**Pager:** 860-588-4505	**E-mail:** David.fiellin@yale.edu
Protocol Correspondent Name & Address (*if different than PI***):** Elizabeth Porter, 367 Cedar Street, Rm 411			
Campus Phone: 737-3347	**Fax:** 737-3306	**E-mail:** elizabeth.porter@yale.edu	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable***):**			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI

o Yes x No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?
o Yes x No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☐ Yale-New Haven Hospital
☐ Cancer Data Repository/Tumor Registry
☐ Specify Other Yale Location:
☐ Yale University PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:

☐ APT Foundation, Inc.
☐ Connecticut Mental Health Center
☐ Clinical Neuroscience Research Unit (CNRU)
☐ Haskins Laboratories
☐ John B. Pierce Laboratory, Inc.
☐ Veterans Affairs Hospital, West Haven
☒ Other Locations, Specify: Veterans Affairs (VAMC), 7 locations: Atlanta GA, Bronx NY, Manhattan/Brooklyn NY, Dallas TX, Houston TX, Los Angeles CA, and Washington DC, Louisiana State University Health Sciences Center.
☐ International Research Site

(Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☒ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Yale University RSC (YU-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ *Nursing Research Committee Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. The expected duration of the study will be 10 years

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☐ Single Center Study
   ☒ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☒ No ☐
   ☒ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☐ **N/A**
   ☐ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☒ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☐ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans

to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒ Pending

Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
   Yes ☐ No☒

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.*

Yes ☐ No☒

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ___ No _X__ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

c. Will a novel approach using existing equipment be applied?

If you answered “no” to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is “pending” at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note “Pending” in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
David A. Fiellin, M.D.	3/6 COMPAAAS U01: INTERVENTION STUDY	National Institute on Alcohol Abuse and Alcoholism (NIAAA)	☒ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☒ Grant-AA020795 ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:
			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To: N/A

Name:
Company:
Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

NOTE: The HIC will remove from the protocol any personnel who have not completed required training.

	Name	**Affiliation: Yale/Other Institution (Identify)**	**NetID**
Principal Investigator	David A. Fiellin, MD	Yale University	Daf7
Role: Co-investigator	Lisa Fucito, PhD	Yale University	Lmf35
Role: Co-investigator	James Dziura, PhD	Yale University	Jdd7
Role: Co-investigator, Project Director	E. Jennifer Edelman, MD, MHS	Yale University	Eje7
Role: Co-investigator	Lynn E. Fiellin, MD	Yale University	Les6
Role: Project coordinator	Evangelia Louizos	Yale University	El244
Role: Data Manager	Laura Simone	Yale University	genovese
Role: Biostatistician	Yanhong Deng	Yale University	Yd59
Role: Biostatistician	Chuqing Chen	Yale University	Cc2499
Role: Co-investigator	Janet Tate, ScD	Yale/VA West Haven	
Role: Co-investigator	Cynthia Brandt, MD, MPH	VA West Haven	

A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV:
PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

_____ _____

PI Name (PRINT) and Signature Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.
- I assume all of the roles and responsibilities of a Principal Investigator even though the student may be called a PI.

_____ _____

Advisor Name (PRINT) and Signature Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____
Chair Name (PRINT) and Signature Date

_____
Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____
YNHH HSPA Name (PRINT) and Signature Date

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

We plan to determine the effectiveness of contingency management (CM) plus stepped care for unhealthy alcohol use in HIV-infected patients. Among HIV-infected patients with unhealthy alcohol use enrolled in the **F**inancial **I**ncentives, **R**andomization with **S**tepped **T**reatment (**FIRST**) trial our **specific aims** and **hypotheses** of the study are as follows:

Aim 1: To compare the efficacy of CM plus stepped care vs. treatment as usual (TAU) on alcohol abstinence as measured using PEth and alcohol consumption using Timeline Followback (TLFB).
Hypothesis 1a: CM plus stepped care will lead to a greater proportion of individuals with PEth documented abstinence.
Hypothesis 1b: CM plus stepped care will lead to fewer self-reported drinks per week by TLFB.

Aim 2: To compare the efficacy of CM plus stepped care vs. TAU on the VACS Index.
Hypothesis 2: CM plus stepped care will lead to a greater proportion of patients who experience at least a 5-point decrease in the VACS Index.

Aim 3 (Exploratory): Among patients with medical conditions adversely impacted by alcohol, to compare the impact of CM plus stepped care vs. TAU on measures including detectable HIV viral load, urine cotinine and anabasine (for smoking cessation), FIB-4, detectable HCV, depressive symptoms and use of psychoactive medications that interact with alcohol.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Patients with unhealthy alcohol use identified by screening are not motivated to stop drinking

Many HIV-infected patients are unaware of the harms associated with their alcohol use.[1] They have stable drinking patterns[2] putting them at ongoing risk for adverse effects from alcohol yet are not motivated to change their drinking. This is especially true among individuals coming for routine medical visits to address other priorities[1] who are identified with unhealthy alcohol use via screening. HIV-infected patients indicate that alcohol consumption serves a number of functions (e.g. coping and facilitating social interactions).[3]

Alcohol use in HIV-infected patients can adversely impact HIV and other medical conditions

Unhealthy alcohol use among HIV-infected patients is associated with lower rates of ART initiation, adherence and suppressed HIV viral load.[4-6] VACS research has demonstrated that HIV-infected individuals with unhealthy alcohol use receive lower quality HIV care.[7,8] In addition, alcohol can adversely impact common non-HIV medical conditions such as tobacco use disorder, liver fibrosis, untreated HCV, depression and interact with psychoactive medications.[9-17] Smoking is a leading preventable cause of morbidity and mortality in HIV-infected patients.[18] Among patients on ART, those who smoke lose more life-years to smoking than to HIV.[18] Alcohol use is associated with decreased odds of smoking cessation and is a common precipitant of relapse to smoking in those who attempt to quit smoking.[14] HIV-infected individuals demonstrate liver fibrosis at levels associated with "low risk" drinking.[19] Guidelines from leading medical societies indicate that there is no known safe level of drinking in those with HCV infection.[11] Similarly, alcohol use is associated with worse depression.[9,10,20] Finally, alcohol has adverse interactions with some psychoactive medications including benzodiazepines,

opioids, antipsychotics, antidepressants, sleeping medications and muscle relaxants.[21,22] Due to the adverse impact of alcohol use on HIV and other medical conditions, interventions that address unhealthy alcohol use among HIV-infected patients are likely to improve overall health and are needed.

Contingency management decreases alcohol use, improves HIV outcomes, and is used in the VA

Contingency management (CM) is an efficacious treatment for individuals with substance use disorders.[23,24] In line with operant conditioning, CM typically provides reinforces (rewards) contingent upon attaining specified goals such as decreased substance use and/or abstinence. A meta-analysis of CM showed an overall effect size (*d)* of 0.42 (medium range) across 47 studies.[23] CM has demonstrated efficacy in decreasing use of a range of substances in uninfected populations and in improving linkage to care, retention in care among and ART adherence in HIV-infected patents.[23-32] The VA has recognized CM as an evidence-based treatment and in 2011 the Deputy Undersecretary of Health for Operations and Management authorized funding for implementation within the VA. Dr. Nancy Petry, a consultant on the current proposal, has been instrumental in working with the VA to implement CM programs,[33] and more than 90 addiction specialty clinics have adopted such programs to address substance use for thousands of patients. Thus, the VA is receptive to using CM indicating our findings may have implications throughout the VA and other health systems.

Integrated and stepped care models for addiction treatment in HIV settings are feasible and effective

Integrating addiction treatment into HIV clinics helps address the challenge of adherence that can occur when patients are referred for off-site services.[34] Our recent work outlining the implementation of integrated alcohol treatment care by Social Workers, Psychologists and Addiction Psychiatrists in 5 VA HIV clinics demonstrates the feasibility and acceptability of this model.[35]

Stepped care strategies help tailor therapy to patient needs. If initial interventions are unsuccessful, treatment intensity is escalated for treatment non-responders.[36] This "self-correcting" property reserves more intensive therapies (stepping-up) for those patients who need them, thereby making the most efficient use of resources.[37] Since the efficacy of CM for alcohol in HIV clinics is unknown, we will step up patients who do not respond to CM at 3 months to care from an Addiction Psychiatrist and MET.

Abstinence is an appropriate target for many HIV-infected patients with unhealthy alcohol use

Progress towards abstinence from alcohol is recommended for patients with AUD, untreated HCV, and liver fibrosis and recent research demonstrates increased mortality risk among HIV-infected patients who consume more than 1 drink per day.[38-40] We have opted to use abstinence as a drinking target, the criterion for stepping up care and the primary outcome for all participants in the proposed trial, based on recent literature documenting the impact of low levels of alcohol consumption on HIV-infected individuals and their greater sensitivity to alcohol's effects compared to uninfected individuals.

Phosphatidylethanol (PEth) is a valid objective index upon which to base CM reinforcement

Phosphatidylethanol is a direct marker of alcohol with high specificity for alcohol abstinence that modestly correlates with dose of alcohol.[41,42] We have elected to use PEth as our primary biomarker for alcohol, instead of other biomarkers such as carbohydrate deficient transferrin, breath alcohol or ethylglucuronide, because it is a direct marker of alcohol, is not impacted by liver disease or HIV, is easy to collect and has a window of detection that is feasible for research and care in HIV clinics.[43-45] PEth is an abnormal phospholipid produced in cell membranes, independent of liver function, by a reaction between ethanol and phosphatitdlycholine.[46] PEth, therefore, is only present on the red blood cells of individuals who have recently consumed alcohol. Consuming 1 drink per day for 6 to 7 days results in PEth that can be detected for 14 to 21 days. Clinically, PEth testing is easily conducted using dried blood spots and sent off for analysis using liquid chromatography with tandem mass spectrometry.[44,47] PEth has been validated in men and women, and patients with HIV and HCV infection.[43,44,47]

A PEth value of <8 ng/ml is consistent with abstinence from alcohol in the past 21 days. While a variety of PEth cut-offs have been proposed, none uniformly correlates with lower risk drinking, at-risk drinking or heavy drinking.[41,48] Research using collateral reports and daily breathalyzers in HIV-infected patients shows PEth has a sensitivity of 88% and a specificity of 89% for any alcohol use in the past 21 days using a cut-off of <10 ng/ml.[44] For the proposed study, we will restrict study entry to those with PEth values >20 ng/ml. We have chosen >20 ng/ml to ensure significant baseline alcohol consumption. We will use PEth <8 ng/ml as our primary efficacy endpoint and to determine eligibility for CM rewards as it reliably reflects abstinence, allows a minimum of a 12 ng/ml decrease to indicate a beneficial change and minimizes false negatives results.[47]

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

Study Overview

The proposed study is a 7 site randomized clinical trial with a 6-month intervention and a total of 12-month follow-up from enrollment, to evaluate the effect of CM plus stepped care on PEth, self-reported drinking, HIV biologic markers (VACS index) and measures for medical conditions impacted by alcohol in HIV-infected patients with unhealthy alcohol use (See Figure). We have chosen 6-months of intervention to allow adequate time to determine a response to CM, the impact of subsequent stepped care in those who do not respond to CM, and to see changes in HIV outcomes. Follow-up at 9 and 12 months allows us to assess the durability of observed changes. The CM intervention will be manual guided and tailored to HIV-infected patients. Three hundred forty-eight patients will be randomized to either CM plus stepped care or TAU.

Inclusion criteria:

1. Be HIV-infected.
2. Recent significant alcohol consumption as determined by a PEth greater than 20 ng/ml.

3. Able to provide informed consent.
4. Meet any of the following criteria for unhealthy alcohol use:
   a. At-risk Drinking – greater than 14 drinks per week or greater than 4 drinks per occasion in men and greater than 7 drinks per week or greater than 3 drinks per occasion in women and those over 65.[49]
   b. Medical condition impacted by alcohol as evidenced by one of the following: 1) detectable HIV viral load (>200 copies/ml),[50] 2) smoked at least 100 cigarettes in their lifetime and who now report smoking cigarettes every day or some days and have a positive exhaled CO test or positive cotinine urine test, 3) detectable HCV virus, 4) liver fibrosis with a FIB-4 >1.45,[51] 5) Patient Health Questionnaire (PHQ-9, validated measure for depression) score greater than 9,[52] or 6) current (at least 30 day supply in the past 60 days) prescription for a psychoactive medication that interacts with alcohol-including benzodiazepines, opioids, antipsychotics, antidepressants, sleeping medications, and muscle relaxants.[21]
   c. Alcohol Use Disorder – Meet DSM-5 criteria for alcohol use disorder, not in remission.[53]

Exclusion criteria: No subject may:
1. Be acutely suicidal, or with an active psychiatric condition that affects his/her ability to provide informed consent or participate in counseling interventions (e.g. psychotic, dementia, delusional).
2. Be currently enrolled in formal treatment for alcohol (excluding mutual-help, e.g. Alcoholics Anonymous)
3. Have medical conditions that would preclude completing or be of harm during the course of the study.
4. Be a pregnant or nursing woman or women who do not agree to use a reliable form of birth control.
5. Have a current diagnosis of or be in remission for a gambling disorder given the gaming nature of CM based on positive screen to the item "Have you ever tried to stop or reduce gambling because it was causing you problems?" followed by >4 positive criteria on the National Opinion Research Center DSM Screen for Gambling Problems (NODS).

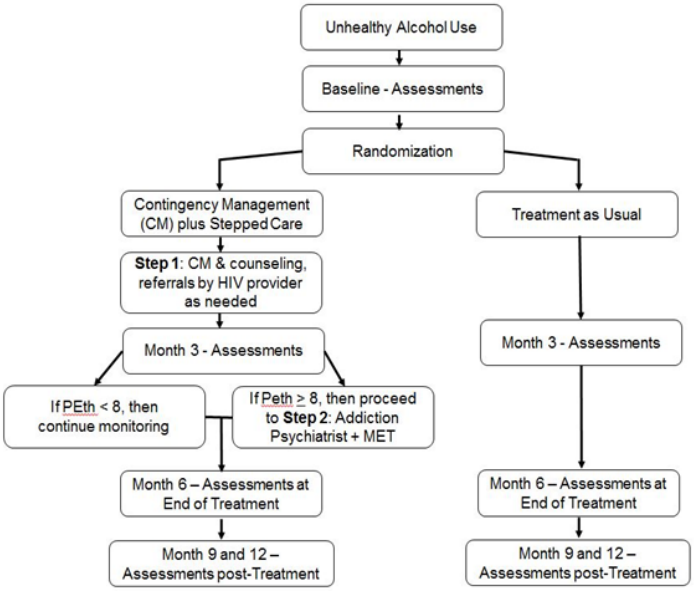

Figure. FIRST Trial: Protocol Overview

Procedures and design

Pretreatment

Screening and referrals. All patients in the 7 HIV clinics undergo annual screening by clinicians for alcohol use via the AUDIT-C by mandate of the VA.[54,55] We have found it useful in prior VA studies to use a multi-pronged approach to recruitment.

a. Direct recruitment of patients: We will receive direct support from the COMpAAAS Resource in Informatics and Biostatistics (RIB), an NIAAA-funded core led by Drs. Cynthia Brandt and Janet Tate, which provides research support to ongoing collaborations within COMpAAAS, with highest security protections and occurring behind the VA firewall and with data access restricted to a limited number of specified and approved research personnel. Specifically, based on electronic health record (EHR) data available through RIB (e.g. labs, diagnoses, medications and visits), we will conduct proactive recruitment, identifying potentially eligible patients via the electronic health record (EHR). The clinic director or providers will be given a list of all their HIV-positive patients for review to identify those who would not be eligible based on above exclusion criteria. To HIV-positive patients in the clinic at each of the participating sites who are deemed appropriate by their provider and/or clinic director, we will mail an introductory letter about the study and signed by their provider and/or clinic director informing them that:

    1) a research study is taking place in the clinic for which they might be eligible,
    2) someone from the study team will be calling them to tell them more about the study and potentially invite them to participate, and
    3) providing them with a number they can call to opt-out of further contact.

    Patients who do not choose to opt out of further contact will be called by a research assistant after two weeks and using a screening script, provided study details, screened for eligibility (i.e. AUDIT-C >0), and if potentially eligible, invited for a pretreatment assessment.[56]

b. Flyers in the clinic: We will develop recruitment materials, similar to those we have used in earlier VA trials on alcohol with HIV-positive patients, for patients and providers. This will allow patients to call the study team directly (self-refer) and be referred by their providers.

c. Referral by providers: Providers can request permission to give a patient's name to study staff; or provide study information to patients in order for the patient to contact the study staff directly.

    1) Providers will be invited to refer patients they feel might be eligible for the study, using a script and information sheet (to be developed and submitted for approval at a future date).

    As an aid to providers, study staff will review daily schedules and remind staff and providers to let patients who are likely to meet eligibility criteria (based upon AUDIT-C screening results and HIV status) know about the study. Providers will be given a reminder card regarding study eligibility criteria and the referral protocol.

d. In-person AUDIT-C: Patients presenting to clinic will be administered an AUDIT-C by research staff or in the context of routine clinical care. Those with an AUDIT-C>0 and potentially eligible will be invited for a pretreatment assessment.

Eligibility Assessment: We will review the patient electronic medical record to assess for the presence of the following: detectable HIV (>200 copies/mL) and/or HCV viral load; FIB-4>1.45 based on labs during the past 60 days; receipt of a psychoactive alcohol-interacting medication. For potentially eligible patients, we will obtain written informed consent for screening. We will then conduct an AUDIT-C. For patients with an AUDIT-C>0, we will assess for the presence of a gambling disorder with the screening item, "Have you ever tried to stop or reduce gambling because it was causing you problems?". For individuals who report "yes", we will complete the National Opinion Research Center DSM Screen for Gambling Problems (NODS) to assess for a gambling disorder. We have opted to use this approach as most all prize Contingency Management studies conducted in the past 10 years have only excluded participants who have tried (or who are actively trying) to quit gambling pathologically. The rationale for not excluding participants who are gambling and who do not desire to reduce or stop their gambling is that CM may help with their substance use problems. Further, there is no evidence to suggest that CM will aggravate or precipitate gambling problems.[57,58] If we were to exclude all heavy or problem gamblers from the study, we would be excluding a fairly high percentage of potential participants, reducing generalizability of the findings and possibly withholding a potentially efficacious intervention for their substance use problems.

For those patients who do not meet criteria for a Gambling Disorder, we will proceed to have patients complete a self-administered online Timeline Followback to assess the past 21 days of alcohol use. Patients who drink an average of at least 7 drinks per week, will proceed with further screening. This may include a mini-SCID to assess for alcohol use disorder (among patient with an AUDIT-C>4) (strong correlation with AUD) [59]); a PHQ-9 to assess for depressive symptoms; and an assessment for smoking. Patients not otherwise meeting criteria who have not had labs drawn within the prior 60 days, may be asked to have an HIV viral load, HCV (antibody or RNA as indicated) and/or necessary labs to determine whether they have evidence of liver scarring by FIB-4 (AST, ALT, and platelets, FIB>1.45).

Consent for PEth: Potentially eligible patients who are HIV-positive, able to provide informed consent and meet any of the criteria for unhealthy alcohol use, and none of the exclusion criteria will be asked to undergo a PEth analysis.

Consent to enroll: If the PEth is > 20 ng/ml patients will asked to provide written informed consent for study participation and enroll in the trial.

Randomization: Eligible participants will be randomly assigned to CM plus stepped care or TAU by the Yale Center for Analytic Sciences (YCAS). Participants will be randomized using a stratified randomization procedure with stratification by site and drinking category (at-risk, medical conditions impacted by alcohol, AUD) as they may be associated with outcomes. We have implemented this process in prior studies.[60,61]

Treatments

Table 2. Comparison of CM plus stepped care and Treatment as usual (TAU)

Step	Treatment Service	CM	TAU
1	Referrals as needed by HIV provider	Y	Y
1	CM counseling	Y	N
1	Reward for PEth < 8 ng/ml	Y	N
1	Reward for addressing medical conditions impacted by alcohol	Y	N
2	Addiction Physician Management	Y	N
2	MET	Y	N

CM plus stepped care arm

Counseling Overview

CM will be provided according to established principles and procedures.[25-27] These include using: 1) contracts that identify target behaviors (e.g. abstinence), 2) objectively quantified behavioral outcomes (breathalyzer or saliva test and PEth), 3) valued rewards, 4) successive approximations to reward progress toward goals, and 5) withholding rewards when target behaviors are not achieved.[26,27]

Contingency Management Visits and Procedures

CM for alcohol will be adapted from prior research.[32] The COMpAAAS RIB will design a web-based program to track CM visits and rewards. CM visits will occur every 3 weeks to correspond with the time frame of abstinence detected by PEth. This will help to minimize patient demands with respect to clinic visits. CM visits will be provided by clinic Social Workers and will occur once every 3 weeks over 3 months (4 sessions). Rewards will be obtained through "draws" of paper slips from a bowl (fishbowl). The slips in the bowl will be set up in accordance with preset (See below) probabilities of rewards. For the VA sites, the rewards will be provided as VA coupons in specific dollar amounts that can be used to purchase items at a VA Canteen store (similar to Walmart and Target stores). This strategy has been used successfully in CM programs in the VA.[33] At the beginning of treatment, the Social Worker will visit the local Canteen store with patients and have them identify items that they wish to purchase with their rewards. For the non-VA site, the research coordinator will add any funds rewarded to a ClinCard.

The bowl from which patients will draw will contain 100 slips of paper. Twenty slips will state "Good job" but not be associated with any tangible earnings. Sixty-four of the slips will state "Medium Prize" and be associated with a $5 reward, 15 will state " Large Prize" and be associated with a $25 reward, and one will state "Jumbo Prize" and be associated with a $100 reward. For VA sites, dollar amounts earned will relate to coupons for use at the local VA Canteen store. For the non-VA site, dollar amounts will be added to a reloadable ClinCard.

At each CM visit, patients will undergo a blood alcohol content analysis (BAC) with a breathalyzer or saliva test and provide a finger stick blood sample for PEth testing. The research coordinator will take a digital photo of the bloodspot collection card. The photo, which will not contain and identifiers (the study ID only) will be sent to the Yale Coordinating Center for approval. Once the sample is approved, the research coordinator will then ship the sample to the lab for testing. The BAC and PEth results will determine whether patients receive rewards for abstinence. Since PEth testing cannot take place onsite, PEth results will available within 72 hours.

Due to the declared public health emergency in March 2020, the CM counseling portion of these 'visits' are done by videoconference or telephone. This will limit participants' and employees' exposure to COVID-19. Participants will be notified that we will not be issuing rewards for PEth and BAC until such time as it becomes safe to do so. However, when it is safe to resume in-person visits, we will resume PEth testing (dried blood spot) and replace the BAC with alcohol saliva tests to reduce any risk of aerosol to study staff.

Rewarding alcohol abstinence
Patients who provide a BAC or saliva test that is negative for alcohol (<0.003 g/dl) will get at least one opportunity to draw a slip of paper from the bowl and earn a monetary amount. The first draw may occur at the baseline visit to expose patients to the fishbowl. Whatever they earn from their BAC or saliva test draw(s) ($5, $25 or $100) will be awarded immediately. They will earn at least one draw for each scheduled BAC or saliva test that tests negative, and draws earned will escalate by one draw for each successive negative BAC or saliva test submitted. In total, patients can earn 14 draws for submitting negative BACs or saliva testsover the 12-week CM treatment phase (Appendix 3).

If a patient's PEth test from an index visit is also negative (<8 ng/ml), he/she will also receive earnings. For the first PEth negative sample, patients will earn 5 draws, and the number of draws earned will increase by one for each successive negative PEth sample provided. Although they will be awarded earnings immediately for the BAC/saliva test negative samples, the PEth takes 3 days to process, and these actual earnings will be awarded when the PEth result becomes available. So long as the BAC or saliva tests negative, the patient will make their PEth draws at the in-person CM session (range 5-8 additional draws). Thus, patients will know that they will earn the amount drawn if the PEth is negative. If the PEth result is positive (>8 ng/ml), then the amounts from those draws will be forfeited (but the patient will still retain the amount earned from the draws for a negative BAC). The Social Worker will notify the patient via telephone of the PEth result and amount being credited based on the value of the slip that was drawn at the CM session. In total, patients can earn up to 26 draws over the 3 months of CM if all 4 of their PEth readings are negative.

If a BAC or saliva tests >0.003 g/dl, then no draws will be awarded that day. The number of draws possible for the next negative BAC or saliva test will reset to one, and the number of draws possible for the next PEth negative sample will reset to 5. After a reset, draws for both negative BACs and PEths will increase as before. Patients testing positive for a BAC or saliva test or PEth will be counseled to abstain from alcohol use and reminded of the draws possible for the next negative BAC and PEth. Any patient who tests above the legal limit for alcohol will be escorted to a unit capable of retaining him/her or allowed to contact a family member who can transport the patient home.

Rewarding addressing medical conditions impacted by alcohol and alcohol treatment goals
In addition to drawing slips for providing a negative BAC or alcohol saliva test and PEth, CM patients will also be able to earn drawings for demonstrating progress toward addressing a medical condition impacted by alcohol or completing specific activities related to attaining abstinence. At the first CM counseling session (See below), the patient will sign a contract

targeting control of a medical condition impacted by alcohol or identifying specific alcohol treatment activities. Medical condition goals will be tailored to the patient's status and medical conditions and could include initiation of or improved adherence to ART (assessed using the VA EHR and the Medication Possession ratio[62-64]), completion of a smoking cessation education session, receipt of smoking cessation medication, or negative exhaled CO testor negative cotinine urine sample, initiation of HCV treatment, or initiation of an antidepressant. We have elected not to reward elimination of psychoactive medication that can interact with alcohol, as this would require a more comprehensive review of risks and benefits than possible in the current trial. Alcohol treatment goals will include completion of online alcohol counseling modules, and for those with AUD, receipt of alcohol pharmacotherapy, attendance at an Alcoholics Anonymous (A.A.) meeting or finding an A.A. sponsor. One specific activity will be set at each visit with objective index of verification specified. The RA will verify these activities through VA EHR or documentation agreed upon in advance.[65,66] Patients will earn a minimum of 3 draws for each activity completed. Draws for completing activities will increase by one for each consecutive activity completed. If a patient fails to complete (or verify) an activity between visits, the number of draws earned will reset to 3 for the next week an activity is completed. These draws will be from the same bowl outlined earlier, and earnings will be awarded immediately upon verification of the activity. In total patients can earn up to 18 draws for completing 4 activities during the 3 months. In total, they can earn a maximum of 58 draws if they complete all 4 activities and submit all negative BACss/alcohol saliva testand PEth, resulting in an average overall maximum of $461 in earnings, consistent with other successful 12-week CM protocols.[25,27,33,66]

Contingency Management Counseling

CM counseling will be manual-guided therapy[27] provided by trained clinic Social Workers. The content of the CM will be adapted to address alcohol use and HIV-infection. Our team has made similar adaptations to incorporate HIV-relevant content to the MET and Brief Interventions manuals in the current **STEP** Trials.

Addiction Physician Management (APM) and Motivational Enhancement Therapy (MET)

Patients in the CM plus stepped care arm who have PEth > 8 ng/ml at 3 months will progress to Step 2 and receive onsite treatment from an Addiction Psychiatrist (APM) and MET from the Social Worker in the HIV clinic. APM will provide care that is typically provided by physicians in specialty referral programs. We have used this model successfully in earlier trials.[35,67] After an initial 45-minute evaluation session, the physicians will administer APM weekly for 2 weeks, every 2 weeks for 4 weeks and then monthly. The physician will 1) assess the impact of alcohol use on medical, psychiatric, social, employment, and legal functioning, 2) educate the patient about alcohol, 3) prescribe alcohol pharmacotherapy if indicated, 4) encourage abstinence and adherence to medication (as appropriate); 5) encourage lifestyle changes, avoidance of triggers and attendance at mutual-help groups; 6) identify and address medical complications of alcohol use; and 7) refer patients to indicated treatment services (e.g., vocational, housing or social service). Medications are useful adjuncts to counseling in initiating abstinence and preventing relapse in patients with AUD. Disulfiram, oral naltrexone, injectable naltrexone, and acamprosate are available at the seven sites. Naltrexone has the best evidence of efficacy and[68] we have demonstrated the safety of naltrexone in HIV-infected patients.[69] In addition, we have completed a trial of injectable naltrexone in HIV-infected heavy drinkers. We allow the

physicians flexibility with respect to choice of pharmacotherapy for a more "real world" implementation. Decisions to not offer alcohol pharmacotherapy for those with AUD will be discussed on a case by case basis with Dr. Edelman or Fiellin in light of contraindications.[70] In addition, monthly supervision phone calls will encourage use of pharmacotherapies where appropriate. The prescribing physicians will have the final decision as to the medication, dose, and duration. Medications will be tracked through assessments and the EHR.

MET will be provided in 4 sessions to coincide with the initial APM visits. At the first MET session with the social worker, participants will be given a personal feedback report which will provide the participants with information on their current drinking habits as well as how their drinking may affect their current health status. We will use the MET manual (based on Dr. Stephen Maisto's [a consultant on the current protocol] ELM Brief Intervention Study Treatment Manual) that we are using in the current **STEP** Trials that includes adaptations for HIV-infected patients. MET is grounded in research on processes of natural recovery during which patients move through stages of change – precontemplation, contemplation, determination, action, and maintenance.[71] The Social Worker's role is to assist the patient in moving through the stages of change. MET uses motivational interviewing and reflective listening to help patients identify internal sources of motivation to support reductions in alcohol. We have selected MET as a counseling platform because 1) it is consistent with the use of alcohol medications, 2) the efficacy is equivalent to other manualized therapies[72] 3) it has applicability to a range of behavioral challenges encountered in medical settings (e.g. diet, smoking), 4) training in motivational interviewing is widely available, and 5) because it has the flexibility to address patients across a spectrum of readiness to change their alcohol use.[73-75]

Due to the declared public health emergency in March 2020, the MET and APM sessions will be done by videoconference or telephone. This will limit participants' and employees' exposure to COVID-19.

Training and supervision of study interventionists

We will use training, structured encounter forms, and ongoing supervision to support treatment fidelity and avoid intervention drift. CM and MET training will be conducted by Drs. Petry, Fucito and Maisto following established manuals and procedures we have used in other NIAAA funded studies.[61,76,77] Initial APM, CM and MET training will occur during a 4-hour session. Our team has extensive experience providing such trainings and conducting faculty development for trainers.[78,79] The overall objectives of the training is for providers to understand and learn to deliver the counseling (CM and/or MET) according to protocol, to avoid techniques that are not part of the counseling intervention, and to ensure that different practitioners use consistent techniques across different cases. Following the initial training, interventionists will be assigned "training cases". Once they have demonstrated proficiency in the counseling technique they will be allowed to treat patients in the study. All training case interventions will be recorded and Drs. Petry and Fucito will review them to assure intervention fidelity. During the study, CM and MET treatment sessions will be recorded and a subset (at least 10%) will be reviewed for fidelity. Dr. Fucito will review audiotapes and provide monthly supervision to the Social Workers providing CM using an adapted Contingency Management Competence Scale.[80] Additionally, CM and MET interventionists will complete content checklists after each session to increase treatment fidelity.

Certified Addiction Psychiatrists at each of the 7 sites have extensive experience providing pharmacotherapy and AUD treatment. APM training will include a review of structured encounter forms, study procedures, protocol adherence, treatment fidelity, review of the Center for Substance Abuse Treatment's guidance on alcohol pharmacotherapies[70] and supervision. Addiction Psychiatrists will participate in monthly supervision calls with Drs. D. Fiellin, Edelman and L. Fiellin.

Criteria for stepping up care (Figure and Table 1)

Consistent with tenets of stepped care designs we provide *a priori* intervals and criteria (drinking targets) that dictate increasing the intensity of treatment (stepping up)[81] based on research and standards in the field. All CM plus stepped care subjects will undergo PEth testing at 3 months to determine the efficacy of Step 1. Patients with a PEth > 8 ng/ml will continue on to Step 2.

Treatment as usual (TAU) arm

We have elected to compare the CM plus stepped care condition to TAU to test its efficacy against a "real world" control and because CM plus stepped care is a comprehensive stand alone intervention that would substitute for TAU.[82] Subjects randomized to receive TAU will not receive targeted psychosocial or pharmacologic intervention from study participation. None of the 7 HIV clinics have fully integrated counseling and pharmacotherapy for alcohol. Primary care providers will be notified if patients meet criteria for an AUD. In addition, TAU subjects will receive a handout with a listing of alcohol treatment services within their VA, alcohol information embedded within general health related information (diet, smoking cessation, ART adherence) and referrals as provided by their primary provider. All patients will be provided with information about and access to the NIAAA informational website (rethinkingdrinking.niaaa.nih.gov) and online counseling that has been used in prior research (www.alcoholfree.info).[83] While annual AUDIT-C screening is mandatory at the 7 sites, providing interventions for patients with unhealthy alcohol use is a matter of physician judgment and individual clinical practice with wide practice variation.[84,85] HIV clinicians will not receive knowledge of the results of follow-up research assessments. We will conduct a Treatment Services Review[86] at each follow-up to assess for receipt of addiction treatment services received since the last assessment and assess for the use of ancillary services.

Assessments

Overview

We will measure a range of pretreatment variables at baseline to ensure that participants meet eligibility criteria and that important predictor variables are measured (Table 3, Summary of Study Assessments). The baseline interview will include evaluations for alcohol, drug, and psychiatric disorders, and verify past 30-day laboratory values or collection of blood work (See Table 3). To avoid assessment reactivity,[87,88] alcohol questions will be as brief as possible and interspersed among questions addressing other health-related domains. Using validated instruments at baseline, during treatment, and at end-of-treatment, we will examine the differential impact of CM plus stepped care on a range of measures. To minimize assessment reactivity, we will restrict assessments to those necessary and attempt to avoid those that would serve as motivation to change alcohol consumption. The primary study outcome, assessed at 6 months, was originally proportion of patients with PEth documented abstinence since this objective measure has advantages over self-report.[89] However, due to difficulty collecting PEth

during the COVID-19 pandemic, and on the recommendation of our DSMB, we changed the primary outcome to self-reported Timeline Follow Back at week 24. Abstinence confirmed by PEth was changed to a secondary outcome, Secondary study outcome, assessed at 3 months, will be proportion of patients with PEth documented abstinence. In addition, we will assess, at 6 months, alcohol consumption by TLFB and change in HIV biological markers as measured by viral load and VACS index. Exploratory analyses will evaluate the impact of CM plus stepped care on measures of medical conditions impacted by alcohol including exhaled CO , FIB-4, detectable HCV infection, depressive symptoms using the PHQ-9 and use of psychoactive medications that interact with alcohol.

Retention and Collection of Patient Locator Information

We use retention and tracking strategies developed to minimize attrition.[90,91] We will obtain locator information on 5 individuals and update at each visit. RAs will notify patients by phone, text, mail and/or email before each assessment. We will contact other locators after 3 attempts and if unsuccessful we will send a registered letter. We couple research visits to scheduled medical visits when possible.

Study Period:

The treatment period will be 6 months with follow up at 12 months. This will allow time for patients' treatment to be stepped up if necessary and to detect differences in alcohol consumption and biologic markers (e.g. VACS index, CD4 lymphocyte counts, and HIV viral load) that may emerge from treatment. Given the cycles of cessation and relapse to prior drinking patterns with alcohol treatment, effects may not persist.[68,92,93] Thus, we plan follow-up assessments at 9 and 12 months. Future chronic care trials may be warranted.[92-96]

	BL	Wk 12	Wk 24	Month 9	Month 12
PEth Testing	**X**	**X**	**X**	**X**	**X**
Web-based Timeline Followback (TLFB) for alcohol	**X**	**X**	**X**	**X**	**X**
AUDIT-C	**X**				
NIAAA single item screen for alcohol use	**X**				
Gambling Disorder assessment (for eligibility)	**X**				
NODS (for all patients upon enrollment)	**X**				
VACS Index – HIV biomarkers (CD4, HIV viral load), creatinine, hemoglobin, FIB-4 components (AST, ALT, platelets), HCV serology and RNA	**X**	**X**	**X**	**X**	**X**
ART medication adherence by pharmacy data	**X**	**X**	**X**	**X**	**X**
HIV risk-taking behavior scale (HRBS)	**X**	**X**	**X**	**X**	**X**
Addiction Severity Index-Lite	**X**		**X**		**X**
ASSIT-Lite (to assess for substance use)	**X**	**X**	**X**	**X**	**X**
Mini-SCID alcohol (only if AUDIT-C greater than 4)	**X**				
Breathalyzer test (BAC) or alcohol saliva test	**X**	**X**	**X**	**X**	**X**
PHQ-9	**X**	**X**	**X**	**X**	**X**
Smoking assessment, including Fagerstrom Test for Nicotine Dependence and e-cigarette use	**X**	**X**	**X**	**X**	**X**
, Exhaled CO (*among people who smoke only) or urine	**X**	**X**	**X**	**X**	**X**

cotinine test					
Treatment Services Review	X	X	X	X	X
Urine pregnancy test, also clinically as indicated	X				
Healthcare utilization (ED visits, ID visits, hospitalization, counseling, intensive outpatient programs, detoxification)	X	X	X	X	X
Medications for alcohol and tobacco use disorder	X	X	X	X	X
Medications for depression	X	X	X	X	X
Medications for hepatitis C virus infection	X	X	X	X	X
Psychoactive medications that potentially interact with alcohol (benzodiazepines, opioids, antipsychotics, antidepressants, sleeping medications, muscle relaxants)	X	X	X	X	X
HIV History	X				
Readiness to change ruler	X				
Family history	X				
Neurocognitive assessment (TRAILS A, TRAILS B)	X	X	X	X	X
Sleep related impairment and sleep disturbance scales	X	X	X	X	X
Patient satisfaction survey		X	X	X	X

Baseline and in-treatment assessments (Table 3)

Summary of Study Assessments

Peth Testing: Self-reports of alcohol consumption will be verified using PEth biomarker which has been validated in HIV-infected and uninfected patients.[43,97-101]

Alcohol consumption will be assessed using a web-based 30-day Timeline Followback (TLFB).[102]

HIV Biomarkers will include components of the VACS Index, CD4 lymphocyte counts and viral load.

ART medication adherence data from the VA EHR will be provided by the COMpAAAS RIB and will be measured using pharmacy fill/refill data using the medication possession ratio (MPR) defined as the (total days supply/refill interval). The MPR is a commonly used validated metric.[63,103-106] For the non-VA site, prescriptions for ART will be tracked through medication order in the Epic system.

The HIV Risk-Taking Behavior Scale (HRBS)[107] is a validated instrument for HIV risk behaviors.

The Addiction Severity Index (ASI) will be used to assess severity of drug- and alcohol-problems, psychiatric symptoms, and medical, employment, legal and social problems over the past 30 days.[108]

The Patient Health Questionnaire (PHQ-9) is a validated depression module of the PRIME-MD that scores each of the 9 DSM-IV depression criteria as "0" (not at all) to "3" (nearly every day).[52]

The Treatment Services Review (TSR), is a validated brief structured interview designed to collect information on the type and amount of treatment services received by the patient in the clinical trial.[86] We will supplement this with treatment service use, including pharmacy fill/refill data (e.g. medications for alcohol and tobacco use disorders, depression, HCV and medications which potentially interact with alcohol), diagnoses, clinic visits and hospitalizations, treatment for alcohol use disorders (e.g. counseling, intensive outpatient program), and laboratory data for the VA sites will be provided by the COMpAAAS RIB.

Assessment of medical conditions impacted by alcohol, for those with tobacco use disorder we will assess exhaled CO or urine cotinine and assess for virologic response in those who entered the trial with untreated HCV, and catalogue past 30 day prescription of psychoactive medications that interact with alcohol assessed through the EHR.

Patient satisfaction survey, based on our prior research, will evaluate patient experience with the study, and for those randomized to CM plus stepped care, components of the intervention.[109]

Follow-up assessments
Assessments at 9 and 12 months will include: PEth testing, pharmacy fill/refill data for ART, TLFB, VACS index, HRBS, ASI, PHQ-9, TSR, exhaled CO test or urine cotinine as indicated, HCV as indicated, past 30 day prescription of psychoactive medications that interact with alcohol. We will additionally assess measures of health care utilization (e.g. ED visits, hospitalizations, medications prescribed) based on the VA EMR or Epic. At the end of study participation all VA subjects will be offered enrollment in VACS for continued follow up.

Due to the declared public health emergency in March 2020, the assessments are done by videoconference or telephone. This will limit participants' and employees' exposure to possible COVID-19 exposure. Participants will receive $50 upon completing the telephone assessment. We will ask participants to complete the visit when conditions permit them to come to the clinic to conduct laboratory and PEth testing.

Participant compensation for completing assessments
Participants will be compensated $50 completing each assessment at baseline assessment, during treatment (3 months), end of treatment (6 months) and the follow-up assessment at 9 and 12-months. The total possible compensation for completing study assessments is $250. Patients randomized to CM plus stepped care patients may earn more depending upon their response to treatment. In addition, patients randomized to CM plus stepped care will receive $15.00 per intervention visit to cover travel costs.

1. Genetic Testing **N/A** ☒

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
ii. the plan for the collection of material or the conditions under which material will be received
iii. the types of information about the donor/individual contributors that will be entered into a database
iv. the methods to uphold confidentiality

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
C. Is widespread sharing of materials planned?
D. When and under what conditions will materials be stripped of all identifiers?
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
    i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?
F. Describe the provisions for protection of participant privacy
G. Describe the methods for the security of storage and sharing of materials

2. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

We will enroll 348 HIV-infected patients with unhealthy alcohol use.

3. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

4. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

<u>Inclusion criteria</u>:
1. Be HIV-infected.
2. Recent significant alcohol consumption as determined by a PEth greater than 20 ng/ml.
3. Able to provide informed consent.

4. Meet any of the following criteria for unhealthy alcohol use:
   a. At-risk Drinking – greater than 14 drinks per week or greater than 4 drinks per occasion in men and greater than 7 drinks per week or greater than 3 drinks per occasion in women and those over 65.[49]
   b. Medical condition impacted by alcohol as evidenced by one of the following: 1) detectable HIV viral load (>200 copies/ml),[50] 2) smoked at least 100 cigarettes in their lifetime and who now report smoking cigarettes every day or some days and have a positive exhaled CO test or urine cotinine test , 3) detectable HCV virus, 4) liver fibrosis with a FIB-4 >1.45,[51] 5) Patient Health Questionnaire (PHQ-9, validated measure for depression) score greater than 9,[52] or 6) current (at least 30 day supply in the past 60 days) prescription for a psychoactive medication that interacts with alcohol-including benzodiazepines, opioids, antipsychotics, antidepressants, sleeping medications and muscle relaxants.[21]
   c. Alcohol Use Disorder – Meet DSM-5 criteria for alcohol use disorder, not in remission

Exclusion criteria: No subject may:
1. Be acutely suicidal, or with a psychiatric condition that affects his/her ability to provide informed consent or participate in counseling interventions (e.g. psychotic, dementia, delusional).
2. Be currently enrolled in formal treatment for alcohol (excluding mutual-help, e.g. Alcoholics Anonymous)
3. Have medical conditions that would preclude completing or be of harm during the course of the study.
4. Be a pregnant or nursing woman or women who do not agree to use a reliable form of birth control.
5. Have a current diagnosis of or be in remission for a gambling disorder given the gaming nature of CM based on >4 positive criteria on the National Opinion Research Center DSM Screen for Gambling Problems (NODS).

5. How will **eligibility** be determined, and by whom?

Participants will be recruited from their clinical sites of HIV care through screening and proactive recruitment. If they are interested, participants will meet with a research assistant who will describe the study in more detail, determine interest in participating, and assess potential eligibility. For potentially eligible patients, the research assistant will obtain written informed consent for screening. All participants' data will be evaluated by the research assistant and the site PI to verify eligibility. Individuals who do not meet eligibility criteria or who decline to take part in the study will be referred to appropriate treatment services. Once the subject has signed the consent, they may withdraw consent at any time.

6. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Potential risks

Patients in the CM plus stepped care arm who get stepped up after the month 3 assessment will receive Addiction Psychiatrist Management. During Addiction Psychiatrist Management, the

Psychiatrist may elect to provide certain FDA-approved medications for the treatment of unhealthy alcohol use. Below we described the potential risks associated with these medications.

Naltrexone, Acamprosate, and Disulfiram:

Naltrexone (NTX) appears to result in greater reductions in alcohol consumption than other pharmacotherapies approved for the treatment of alcohol dependence. For this reason, we will encourage that Addiction Psychiatrists consider the use of NTX if not contraindicated (e.g. concomitant opioid agonist treatment for pain or opioid dependence).

Numerous studies have found NTX to be safe and rarely associated with toxicity or severe side effects. These side effects appear to be dose-related and are less likely to occur at the dose proposed in this study. The most frequently reported side effects are gastrointestinal in nature, including epigastric pain, nausea and vomiting. Other, less frequent side effects include nervousness, headaches, low energy, sweating, joint and muscle pain, blurred vision and insomnia. Hepatotoxicity can occur but typically at much higher doses (e.g., 200-300 mg daily) and resolves when NTX is discontinued. Additionally, case reports have reported elevated liver enzyme tests in patients who were taking non-steroidal anti-inflammatory drugs in combination with high-dose NTX. In this study, physicians will have the option to instruct patients to initiate NTX at a dose of 25mg of oral NTX for 4 days and then 50mg per day. NTX has been shown to have an effect on the embryo in the rat and the rabbit when given in doses approximately 140 times the human therapeutic dose. Thus, we will instruct Addiction Psychiatrists not provide NTX to pregnant or nursing women or those who do not agree to use a reliable form of birth control. Before FDA approval, extended release NTX was studied in more than 900 patients [110]. Extended release NTX appears to be generally well tolerated, and adverse effects tend to be mild [110, 110]. Patients using extended release NTX do not develop tolerance for or dependence on the medication. The extended release formula has been shown to be safe, tolerable, and efficacious in the treatment of alcohol use disorders.[110] In a large 6-month multi-site study in the treatment of alcohol dependence the most common adverse events (AEs) were nausea, headache, and fatigue. Nausea was mild or moderate in 95% of cases; however, the large majority of these cases occurred only during the first month of treatment. The most common injection site reaction was tenderness. A recent large study of extended release NTX found that mean liver enzymes did not change significantly over the course of treatment and there was no effect of medication on the proportion of patients in the different groups who had liver enzyme elevations higher than 3 times the upper limit of normal [110]. In addition, it has been found to be safe for use in patients with mild to moderate liver impairment [110] with evidence of a 15% greater reduction in liver enzyme levels in the NTX group as compared with the placebo group [110].

Based on the existing literature on interactions between NTX and ART, these interactions should be clinically insignificant. Many of the medications used for the treatment of HIV are metabolized via the cytochrome P-450 system (CYP450) leading to issues surrounding drug interactions with a number of medication classes. The metabolism of NTX, however, is not entirely metabolized via CYP450 and therefore significant interactions with ART medications would not be expected [110, 110]. A large multi-center safety study of the use of NTX for alcoholism in 865 individuals, including patients with comorbid psychiatric illness, concomitant medications, polysubstance abuse, and HIV demonstrated that serious side effects in these populations were uncommon [110]. While this study was not randomized in design and was intended to look at medication interactions, the findings are reassuring for patients with HIV

disease. Extended release NTX is approved for use in patients who meet criteria for Childs-Pugh A and B liver disease.

Acamprosate: The most common and persistent side effect of acamprosate is diarrhea. Less common side effects include suicidal ideation, intestinal cramps, headache, flatulence, increased or decreased libido, insomnia, anxiety, muscle weakness, nausea, pruritis, and dizziness. The dose of acamprosate needs to be adjusted based on renal function. Diarrhea can be managed with medications that slow gastrointestinal motility. There are no known medication interactions between acamprosate and ARVs.

Disulfiram: Disulfiram can cause minor side effects that typically occur during the first 2 weeks of therapy and wane either spontaneously or after a decrease in dose. These include acneiform eruptions, headache, allergic dermatitis, impotence, mild drowsiness, metallic aftertaste and fatigue. Hepatic toxicity including hepatic failure have been reported.[110] Severe hepatitis associated with disulfiram may develop even after many months of treatment. Hepatic toxicity has occurred in patients with or without a history of abnormal liver function. Other severe side effects of disulfiram include optic neuritis, neuropathy, and psychosis. Monitoring of liver function, to assess for hepatotoxicity, will be important, especially in HIV/HCV co-infected patients. There are recognized medication interactions between disulfiram and several medications commonly used in HIV+ patients including metronidazole, isoniazid, rifampin, warfarin, benzodiazepines, oral hypoglycemics, desipramine, elavil, dilantin, theophyline that can lead to medication discontinuation or changes in dose. [110]

Interaction of alcohol pharmacotherapies and alcohol: NTX has been shown to reduce the number of drinks consumed in the laboratory and in the clinic. No safety concerns have been identified in these studies when alcohol is consumed in combination with NTX. There is no evidence that individuals attempt to over-ride the effects of NTX by drinking more. NTX does not block the aversive effects of alcohol consumption which serve to limit drinking. Acamprosate, like NTX, can be continued in patient who continue to consume alcohol. Disulfiram, which has been used clinically for more than 60 years, blocks the enzyme aldehyde dehydrogenase resulting in a rapid buildup of aldehyde. This disulfiram-alcohol reaction begins 10-30 minutes after the ingestion of alcohol. The severity of the disulfiram-alcohol reaction varies from moderate to severe and includes nausea, emesis, vertigo, syncope, arrhythmia, and seizure. For this reason, patients who are prescribed disulfiram are instructed to avoid any product containing alcohol, including mouthwash.

Counseling There are no significant adverse effects of participating in the counseling intervention portion of this study provided by the Social Worker or Addiction Psychiatrist. Participation is likely to be of benefit.

Breathalyzer, blood/urine collections: Breathalyzer and blood and urine collections are performed primarily as safeguards and should add no risks other than those normally associated with these procedures.

Rating scales and questionnaires: Rating scales, structured interviews, and questionnaires are all non-invasive, and should also add no risks to subjects, as our past experience indicates.

Recorded sessions: Participants will be made aware during the informed consent process that sessions with the study Social Worker will be digitally recorded and that the nature of these sessions will involve participants speaking about information regarding their health status, alcohol use, HIV status, medical history, and participation in the study. However, participant names will never be recorded on the tapes and the tapes will be coded by participant number rather than name in order to protect participant confidentiality. Participants will be given the option to decline to be taped during the study.

Risks include inconvenience and concerns about confidentiality.

7. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Protection against *risk:*
As the safety of alcohol pharmacotherapy has not been established in pregnant and nursing women, they will be excluded from participation. Women of child-bearing capacity must agree to use a reliable form of birth control. Pregnant women will be referred for other alcohol treatment. Women who become pregnant during the study will be taken off study medications immediately.

NTX: Addiction Psychiatrists will be instructed to avoid prescribing NTX in patients with medical conditions that would contraindicate the use of NTX. We will instruct Addiction Psychiatrists to exclude individuals from receiving NTX if they have evidence of significant hepatocellular injury (AST, ALT > 5 times the upper limit of normal or a diagnosis of cirrhosis and Child-Pugh class greater than A or B). We will instruct Addiction Psychiatrist to monitor liver enzyme tests prior to, during, and at end of treatment and a subject whose AST or ALT rises to > 5 times the upper limit of normal will have laboratory tests repeated in one week. If liver enzymes are persistently elevated or if the individual is symptomatic, we will instruct Addiction Psychiatrists to consider discontinuing NTX and refer patients for a Hepatology evaluation.

Acamprosate: We will instruct Addiction Psychiatrists to avoid prescribing acamprosate in patients with medical conditions that would contraindicate its use. Individuals should not receive acamprosate if they have evidence of renal insufficiency with a creatinine clearance of less than 30 mL/min. For those subjects with a creatinine clearance of 30-50 ml/min physicians can use a reduced dose of 333 mg per day.

Disulfiram: We will instruct Addiction Psychiatrists to avoid prescribing disulfiram in patients with medical conditions that would contraindicate its use. Individuals should not receive disulfiram if they have evidence of severe coronary artery disease or psychosis. There is no known evidence that suggests that patients with preexisting liver disease are more likely to experienced severe hepatotoxicity from disulfiram yet caution should be exercised in those with hepatic decompensation. We will instruct Addiction Psychiatrists to monitor liver enzyme tests prior to, during, and at end of treatment and a subject whose AST or ALT rises to > 5 times the upper limit of normal will have laboratory tests repeated in one week. If liver enzymes are persistently elevated or if the individual is symptomatic, we will instruct Addiction Psychiatrists to consider discontinuing NTX and refer patients for a Hepatology evaluation.

Rating scales and questionnaires The major risk of the assessments is the potential loss of confidentiality which is discussed in the section related to confidentiality below. To minimize any discomfort associated with reporting on sensitive behaviors, participants will be informed that they may refuse to answer questions that they are not comfortable answering. Questions related to eligibility determination and monitoring of safety and treatment response are not optional. If a person declines to answer these questions, we will advise them that they will not be able to participate and we will make a referral to other treatment if they are interested.

Digitally recorded sessions: All appropriate actions will be taken by staff members in order to minimize the risks associated with loss of confidentiality. Audio files will be coded by number and will be erased 6 years after the completion of the study.

Confidentiality: Numerous steps will be taken to protect confidentiality as described under the section on Sources of Materials (E.1.b). In addition, a Certificate of Confidentiality will be obtained from NIAAA. This certificate will protect the confidentiality of all research records generated by this study. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. All research personnel will be trained on Institutional Review Board (IRB) and HIPAA procedures.

In Case of Injury: If a participant is injured as a direct result of participation in this study, treatment will be provided. The participant and/or his or her insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Participants will not waive their legal rights by participating in this study.

8. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

   What is the investigator's assessment of the overall risk level for subjects participating in this study? **Minimal**

   b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? **N/A**

   c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
      i. Minimal risk
      ii. Greater than minimal

The risks associated with participating in this study can be categorized as minimal (i.e., risks are recognized as being similar to everyday risks, and there is adequate surveillance and protections to discover adverse events promptly and keep their effects minimal). We have included in the protocol procedures to exclude participants who would be at the greatest risk (e.g. concomitant significant medical or untreated psychiatric conditions). We will use procedures to detect and respond to adverse events that ensure prompt discovery of any adverse events and to minimize their effects. Consistent with the Data and Safety Monitoring Plan (DSMP) template of the Yale University School of Medicine, the DSMP includes provisions for data review and performance of safety reviews, as described below.

Data and safety monitoring procedures in this study include computerized data collection and monitoring systems and an organizational structure of clearly defined tasks assigned to all research and clinical personnel involved in the conduct of this study. The computerized data collection and monitoring system consists of a data base system that records clinical and research activities, completion of scheduled assessments, and delivers computerized versions of most of research instruments used in this study. Research assistants use this database to monitor and schedule patients and activities and to administer study assessments. Data entry of non-computerized assessments is accomplished by using specialized data entry software (such as, SPSS Data Entry or Microsoft Access Data base) facilitating efficient data entry and allowing elimination of out-of-range values and double entry of data for detection of key punch errors.

The organizational structure used to ensure quality of data in this project include: 1) extensive training and close supervision of research assistants in data collection; 2) preliminary review of all data for completeness and coding errors by data manager/analyst; and 3) utilization of error-checking statistical procedures. Experienced data manager/analysts and the PI supervise data procedures. All error corrections are fully documented in the research records of the study. All research personnel are required to participate in and document training in protection of human subjects and the responsible conduct of scientific research.

Procedures for training and supervision of RAs and audio file raters have been developed as part of our previous and current studies. Initial training utilizes intensive seminars on all of the research instruments, after which the RAs observes the trainer administer the assessments and co-rates the assessments. Subsequently, the RA will conduct the assessments and make the ratings with the trainer present for a minimum of five full assessments and until complete agreement is obtained. During the study, the Project Coordinator, Ms. Louizos will review all assessments and provides feedback on the completeness, accuracy or errors in the rating forms. Continued supervision and training on all instruments is provided on a regular basis to insure continued reliability of the assessments. RAs and tape raters are not involved in the provision of treatment to patients and are not informed about the treatment assignments.

All clinical aspects of the study, such as treatment delivery and monitoring of subjects' progress or the lack of thereof are also fully documented and supervised. The research team meets weekly to review the overall progress of the study, as well as to review digitally recorded sessions and/or discuss progress of each subject in the study. All members of the research team, both research assistants and clinicians, are familiar with procedures for identifying and reporting possible adverse reactions.

All adverse events are reported using the Yale Institutional Review Board (IRB) standard template for reporting adverse events. The Principal Investigator (PI) reviews all adverse events, classifies the attribution of adverse events (e.g., definitely, probably, possibly related; unlikely or unrelated) and grades the severity of the event, utilizing the FDA's definition of serious adverse events, on a 6-point scale (0=no adverse event or within normal limit; 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=fatal). Serious adverse events will be reported within 48 hours to the NIAAA project officer. Serious and unanticipated and related adverse events or unanticipated problems involving risks to subjects or others will be reported in writing within 48 hours to the Yale IRB. A summary of adverse events will be reported annually to the

NIAAA project officer. Reporting of serious and non-serious adverse events will continue during the follow-up phase of the study. The PI will evaluate all adverse events and determine whether the event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (e.g., Risks to Subjects) or consent form (e.g., Risks and Inconveniences) are required.

During the follow-up phase, months 6 to 12, patients requiring additional intervention due to significantly increased alcohol consumption or serious psychiatric/medical symptoms will be referred to appropriate care within their facility.

The Yale Center for Medical Informatics (YCMI) (http://ycmi.med.yale.edu/) will be responsible for data management using a web-based clinical trial management system (CTMS). Study data will be entered into the Web-accessible CTMS. To facilitate data monitoring the CTMS will generate web accessible reports and reminders to help monitor and manage the data collection process. The system can check for data inconsistencies, omissions, and errors regularly. Data questions or problems will trigger data queries and analyses of missing data will be done periodically to assure that all forms are entered and available for analysis. Data Security is achieved via the following methods; 1) CTMS staff will receive HIPAA and Human Subjects Protection training, 2) Users will act in full compliance with HIPAA regulations, and 3) Sensitive data is encrypted. The web data-entry interface allows data entry from anywhere on the Internet and uses 128-bit secure sockets layer security to protect the confidentiality of the data. The CTMS also maintains an electronic audit trail of all modifications to study data. VA Connecticut houses and maintains the security and backup of all servers and workstations. Passwords and personal health information will be encrypted in the database server.

The PI will be responsible for monitoring the data and conducting performance and safety reviews, at the specified frequency. Either the PI or the IRB have the authority to stop or modify the study. The monitoring by the IRB will occur annually at the time of re-approval. The PI will conduct data and safety review at least quarterly and at any time a serious adverse event occurs. During the review process, the PI will evaluate whether the study should continue unchanged, requires modification or amendment to continue, or should be closed to enrollment.

Ismene Petrakis, M.D. will serve as Chair of the Data Safety and Monitoring Board (DSMB) which will be composed of another expert in clinical trials in alcohol treatment and an expert in statistical analysis of clinical trials. Twice annually the DSMB will review the progress of the study and frequency of serious adverse events.

d. For multi-site studies for which the Yale PI serves as the lead investigator:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?

All adverse events are reported using the Yale Institutional Review Board (IRB) standard template for reporting adverse events. The Yale Principal Investigator (PI) reviews all adverse events, classifies the attribution of adverse events (e.g., definitely, probably, possibly related; unlikely or unrelated) and grades the severity of the event, utilizing the FDA's definition of serious adverse events, on a 6-point scale (0=no adverse event or within normal limit; 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=fatal). Serious unanticipated or anticipated adverse

events will be reported immediately to the IRB and to NIAAA. Adverse events will be reported in summary form at least annually to the IRB. The summary will include the number of subjects enrolled and a summary of graded adverse events to date, using the chart format included in the Yale University DSMP template. The PI will evaluate all adverse events and determine whether the event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (e.g., Risks to Subjects) or consent form (e.g., Risks and Inconveniences) are required.

ii. What provisions are in place for management of interim results?

No interim analyses will be performed

iii. What will the multi-site process be for protocol modifications?

There will be one protocol document and each participating institution will utilize that document. The Yale PI is responsible for the coordination of the approval of the protocol as well as its subsequent amendments and will be responsible to ensure that the sites are using the correct version of the protocol. The Yale PI will collect and maintain copies of all IRB approvals from each site and will collect and review conflicts of interest declarations made by the Site PIs.

9. **Statistical Considerations:** Describe the statistical analyses that support the study design.

General considerations: This is a randomized, controlled, parallel group trial to evaluate the effectiveness of CM plus stepped care compared to TAU to reduce unhealthy alcohol use in HIV-infected individuals. Data analysis will be conducted by Dr. Dziura and YCAS. The 6-month follow-up was chosen as the primary endpoint as we expect the most robust differences at this time and there is uncertainty in the shape of the treatment response over time. Average intervention group differences across all time points and slopes of change will be compared between groups in supportive secondary analysis. A type I error of 5% (two-sided) will be used to test for significance and analyses will be performed using SAS v9.2 (SAS Institute, Cary, NC).

Adequacy of sample size

The primary aim of the study is to determine whether CM plus stepped care will lead to a greater proportion of patients with PEth documented abstinence when compared to TAU. The primary outcome will be proportion of patients with self reported abstinence on Timeline Follow Back at 6 months, with PEth < 8 ng/ml at 6 months as a secondary outcome (Aim 1). Data from the TAU group in the **STEP** Trials, when restricted to those with a PEth > 20 ng/ml at baseline, reveals 11% spontaneous abstinence as assessed using PEth < 8 ng/ml at 6 months. We believe this provides a good estimate of the anticipated abstinence rate with TAU in the proposed trial. To detect a 15% difference (proportion demonstrating abstinence in CM plus stepped care of 26%) with 80% power at a two-sided 0.05 significance level, a sample size of 139 per group is required. Thus, we will enroll and randomize 348 patients to account for 20% dropout. Based on alcohol consumption in the TAU arms of the **STEP** Trials, and a standard deviation of 11.5, we will have 80% power to detect a difference of 3.9 in average drinks per week over the last 30 days, at 6 months. Data from the TAU group in the **STEP** Trials reveals that 29% of patients

experienced a 5-point decrease in the VACS Index at 6 months. With the proposed sample size, we will have 90% power, at a two-sided 0.05 significance level, to detect a 20% difference in this (Aim 2) outcome (proportion of patients who achieve a 5-point decrease in the VACS Index in CM plus stepped care of 49%). In our prior trials, including the **STEP** Trials, we have obtained completed 6-month assessments in 74-95% of enrolled subjects.[60,61]

Baseline comparability: Because of the sample size, we expect the randomization process will produce reasonably comparable groups. However, the adequacy of the randomization will be assessed by comparing the distribution of baseline demographic and clinical characteristics among the intervention groups. Comparability for continuous variables will be examined graphically and by summary statistics (means, medians, quartiles, etc.). Categorical variables will be examined using frequency distributions. If we find differences in baseline characteristics, we will conduct a sensitivity analysis employing covariate adjustment.[110]

Interim monitoring: Interim monitoring will focus on recruitment, adherence to protocol, baseline comparability of treatment groups, completeness of data retrieval, and uptake of the assigned intervention. A set of monitoring tables will be generated by YCAS for this purpose. No interim looks for efficacy are planned.

Analysis for Aim 1: The primary objective of the analysis is to determine if the proportion of individuals with self reported abstinence on the Timeline Follow Back differs between those assigned to CM plus stepped care compared to those receiving TAU. Abstinence will be assessed using PEth at 3, 6, 9 and 12 months after randomization as a secondary outcome.

A likelihood-based ignorable analysis using a generalized linear mixed model (GLMM) will be used to compare abstinence between groups.[111,112] The primary advantage of the mixed model when compared to commonly used methods such as complete case analysis and single imputation (e.g. last observation carried forward) is its flexibility in handling missing data. This analysis makes use of all available outcome data at each timepoint and assumes that missing data occurs at random (i.e. not informative).[113] The inclusion of 3, 6, 9 and 12 month outcome data in the model will assist in meeting this assumption. More specifically the mixed models will include fixed effects for intervention (CM plus stepped care vs. TAU), time (3, 6, 9, 12 months), and the interaction of intervention with time. Additional fixed effects will be included for baseline covariates: PEth, stratification group (at-risk drinking, medical condition impacted by alcohol, AUD), number of drinks per week, gender, VACS index and study site. Given the heterogeneity in the patient groups, the interaction between intervention and stratification group will be evaluated and included in the primary analysis at the $p<0.10$ significance level. Linear contrasts will be used to estimate intervention group differences and 95% confidence intervals at the primary 6-month outcome assessment. Similar contrasts will be performed at the other secondary follow-up times and supportive analyses examining the average and slope of change in abstinence rates across post-randomization time will be performed. Subgroup analyses will be performed to evaluate moderation of the intervention response by stratification group and study site. We will also use linear mixed effect models to compare continuous PEth and alcohol consumption using data from the TLFB.

Analysis for Aim 2: The primary objective of Aim 2 is to determine if HIV biomarkers (VACS index) differ between subjects receiving CM plus stepped care compared to those receiving TAU. The primary response will be defined as a 5-point improvement from baseline on the VACS index. As in Aim 1, a GLMM will be used to compare this response. We will use a repeated measures mixed model analysis with continuous VACS index as the outcome. As in Aim 1, we will perform subgroup analyses to evaluate moderators.

Analysis for Exploratory Aims: For aim 3, we will evaluate the impact of the intervention in those with medical conditions on condition-specific outcomes such as HIV viral load, eCO or urine cotinine (for smoking cessation), FIB-4, detectable HCV virus, depressive symptoms and use of psychoactive medications that interact with alcohol. These analyses will focus on estimation rather than hypothesis testing and will be performed only in those identified with the specific medical condition at baseline. GLMMs will be used to describe these outcomes by treatment group and time. Treatment differences for continuous outcomes, odds ratios for dichotomous outcomes and rate ratios for count outcomes along with 95% CIs will be estimated.

Plan for Missing Data: Several strategies will be imposed to accommodate the likelihood of missing data. Prevention is the most effective manner to control bias and loss of power from missing data.[114] In our prior alcohol trials we have obtained 6 month assessments in 95% and 88% of subjects.[60,61] We will follow the intent to treat principle, requiring follow-up of all subjects randomized regardless of the treatment received.[115] Telephone and text visit reminders will be sent to participants prior specified collection times. Timely data entry combined with weekly missing data reports will trigger protocols for tracking and obtaining missing data items. Despite these efforts it is reasonable to assume missing data will occur. Our primary analysis is valid under the assumption that missing data is missing at random (MAR).[111] We will evaluate the plausibility of this assumption by determining the extent of missing data and use logistic regression to identify factors associated with dropout. While we do not expect differential dropout rates between groups or high loss to follow-up, we will perform sensitivity analysis using pattern-mixture and selection models under missing not at random (MNAR) assumptions to examine the robustness of conclusions of the primary analysis to missing data.

Timeline and Milestones

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

All four alcohol treatment pharmacotherapies that may be used at the discretion of the Addiction Psychiatrists have been approved for the indication of treatment for alcohol dependence. These medications are disulfiram, oral NTX, injectable NTX, and acamprosate.

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

a. What is the Investigational New Drug (IND) **number** assigned by the FDA?
b. Who holds the IND?
c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____
Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and
an exemption is being sought, review the following categories and complete the category that applies
(*and delete the inapplicable categories)*: **N/A**

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Potential risks
NTX, Acamprosate, and Disulfiram:
Naltrexone: NTX appears to result in greater reductions in alcohol consumption than other pharmacotherapies approved for the treatment of alcohol dependence. For this reason, we will encourage that Addiction Psychiatrists consider the use of NTX if not contraindicated (e.g. concomitant opioid agonist treatment for pain or opioid dependence).

Numerous studies have found NTX to be safe and rarely associated with toxicity or severe side effects. These side effects appear to be dose-related and are less likely to occur at the dose proposed in this study. The most frequently reported side effects are gastrointestinal in nature, including epigastric pain, nausea and vomiting. Other, less frequent side effects include nervousness, headaches, low energy, sweating, joint and muscle pain, blurred vision and insomnia. Hepatotoxicity can occur but typically at much higher doses (e.g., 200-300 mg daily) and resolves when NTX is discontinued. Additionally, case reports have reported elevated liver enzyme tests in patients who were taking non-steroidal anti-inflammatory drugs in combination with high-dose NTX. In this study, physicians will have the option to instruct patients to initiate NTX at a dose of 25mg of oral NTX for 4 days and then 50mg per day. NTX has been shown to

have an effect on the embryo in the rat and the rabbit when given in doses approximately 140 times the human therapeutic dose. Thus, we will instruct Addiction Psychiatrists not provide NTX to pregnant or nursing women or those who do not agree to use a reliable form of birth control. Before FDA approval, extended release NTX was studied in more than 900 patients [116]. Extended release NTX appears to be generally well tolerated, and adverse effects tend to be mild [117,118]. Patients using extended release NTX do not develop tolerance for or dependence on the medication. The extended release formula has been shown to be safe, tolerable, and efficacious in the treatment of alcohol use disorders [117]

Based on the existing literature on interactions between NTX and ART, these interactions should be clinically insignificant. Many of the medications used for the treatment of HIV are metabolized via the cytochrome P-450 system (CYP450) leading to issues surrounding drug interactions with a number of medication classes. The metabolism of NTX, however, is not entirely metabolized via CYP450 and therefore significant interactions with ART medications would not be expected [119,120]. A large multi-center safety study of the use of NTX for alcoholism in 865 individuals, including patients with comorbid psychiatric illness, concomitant medications, polysubstance abuse, and HIV demonstrated that serious side effects in these populations were uncommon [121]. While this study was not randomized in design and was intended to look at medication interactions, the findings are reassuring for patients with HIV disease. Extended release NTX is approved for use in patients who meet criteria for Childs-Pugh A and B liver disease. While these data are reassuring, monitoring of liver function, to assess for hepatotoxicity, will be important, especially in HIV/HCV co-infected patients. The proposed study will systematically examine the question of medication interactions by closely following for adverse effects.

Acamprosate: The most common and persistent side effect of acamprosate is diarrhea. Less common side effects include suicidal ideation, intestinal cramps, headache, flatulence, increased or decreased libido, insomnia, anxiety, muscle weakness, nausea, pruritus, and dizziness. The dose of acamprosate needs to be adjusted based on renal function. Diarrhea can be managed with medications that slow gastrointestinal motility. There are no known medication interactions between acamprosate and ARVs.

Disulfiram: Disulfiram can cause minor side effects that typically occur during the first 2 weeks of therapy and wane either spontaneously or after a decrease in dose. These include acneiform eruptions, headache, allergic dermatitis, impotence, mild drowsiness, metallic aftertaste and fatigue. Hepatic toxicity including hepatic failure have been reported.[70] Severe hepatitis associated with disulfiram may develop even after many months of treatment. Hepatic toxicity has occurred in patients with or without a history of abnormal liver function. Other severe side effects of disulfiram include optic neuritis, neuropathy, and psychosis. Monitoring of liver function, to assess for hepatotoxicity, will be important, especially in HIV/HCV co-infected patients. There are recognized medication interactions between disulfiram and several medications commonly used in HIV+ patients including metronidazole, isoniazid, rifampin, warfarin, benzodiazepines, oral hypoglycemics, desipramine, elavil, dilantin, theophylline that can lead to medication discontinuation or changes in dose.[70]

Interaction of alcohol pharmacotherapies and alcohol: NTX has been shown to reduce the number of drinks consumed in the laboratory and in the clinic. No safety concerns have been identified in these studies when alcohol is consumed in combination with NTX. There is no evidence that individuals attempt to over-ride the effects of NTX by drinking more. NTX does not block the aversive effects of alcohol consumption which serve to limit drinking.

Acamprosate, like NTX, can be continued in patient who continue to consume alcohol. Disulfiram, which has been used clinically for more than 60 years, blocks the enzyme aldehyde dehydrogenase resulting in a rapid build-up of aldehyde. This disulfiram-alcohol reaction begins 10-30 minutes after the ingestion of alcohol. The severity of the disulfiram-alcohol reaction varies from moderate to severe and includes nausea, emesis, vertigo, syncope, arrhythmia, and seizure. For this reason, patients who are prescribed disulfiram are instructed to avoid any product containing alcohol, including mouthwash.

3. **Source:** a) Identify the source of the drug or biologic to be used.

   Alcohol pharmacotherapies will be provided through routine clinical care by the pharmacies at the 7 Medical Centers.

   b) Is the drug provided free of charge to subjects? ☐ Yes ☒ No
   If yes, by whom?

   Alcohol pharmacotherapies will be provided through routine clinical care according to standard medication benefits. All 4 medications are available and covered by hospital formularies.

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

   Check applicable Investigational Drug Service utilized:

   ☐ **YNHH IDS**
   ☐ **CMHC Pharmacy**
   ☐ **PET Center**
   ☐ **Other:**
   ☐ **Yale Cancer Center**
   ☐ **West Haven VA**
   ☒ **None**

   Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. **Use of Placebo:** ☒ **Not applicable to this research project**
   If use of a placebo is planned, provide a justification which addresses the following:
   1. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.
   b. State the maximum total length of time a participant may receive placebo while on the study.
   c. Address the greatest potential harm that may come to a participant as a result of receiving placebo.
   d. Describe the procedures that are in place to safeguard participants receiving placebo.

6. **Use of Controlled Substances:**

Will this research project involve the use of controlled substances in human subjects?
☐ Yes ☒ No *See HIC Application Instructions to view controlled substance listings*.

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure** ☐ **Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☒ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. Patients will be encouraged to follow-up with their medical providers and/or seek additional services upon completion of study enrollment as indicated to continue medications for unhealthy alcohol use.

☐ No If no, explain why this is acceptable.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No *If Yes, please be aware of the following requirements*:

a. A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary, " and attach any other pertinent documents. Then select "save and submit" to submit your request**; and

b. Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. What is the name of the device to be studied in this protocol?

Has this device been FDA approved? ☐ Yes ☐ No
If yes, state for what indication.

3. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

4. **Source:**
   a) Identify the source of the device to be used.

   b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

☐ **Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?

Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

Who holds the IDE?

☐ **Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions,* Section VI.B.4 at http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf *to determine if these pertain to this study.*

☐ **Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. **Investigational device accountability**:
   a. State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

      Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. targeted for enrollment at Yale for this protocol 0

b. If this is a multi-site study, give the total number of subjects targeted across all sites 348

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

- ☒ Flyers
- ☐ Posters
- ☒ Letter
- ☒ Medical Record Review
- ☐ Departmental/Center Newsletters
- ☐ YCCI Recruitment database
- ☐ Internet/Web Postings
- ☐ Mass E-mail Solicitation
- ☐ Departmental/Center Website
- ☐ Departmental/Center Research Boards
- ☐ Web-Based Clinical Trial Registries
- ☒ Clinicaltrials.gov Registry (do not send materials to HIC)
- ☐ Radio
- ☐ Telephone
- ☐ Television
- ☐ Newspaper
- ☒ Other (describe): HIV providers at each site

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

a. Direct recruitment of patients: For recruitment of VA patients,w e will receive direct support from the COMpAAAS Resource in Informatics and Biostatistics (RIB), an NIAAA-funded core led by Drs. Cynthia Brandt and Janet Tate, which provides research support to ongoing collaborations within COMpAAAS, with highest security protections and occurring behind the VA firewall and with data access restricted to a limited number of specified and approved research personnel. Specifically, based on electronic health record (EHR) data available through RIB (e.g. labs, diagnoses, medications and visits), we will proactive recruitment, identifying potentially eligible patients via the electronic health record (EHR). The clinic director or providers will be given a list of all their HIV-positive patients for review to identify those who would not be eligible based on above exclusion criteria. To HIV-positive patients in the clinic at each of the participating sites who are deemed appropriate by their provider and/or clinic director, we will mail an introductory letter about the study and signed by their provider and/or clinic director informing them that:

1. A research study is taking place in the clinic for which they might be eligible,
2. Someone from the study team will be calling them to tell them more about the study and potentially invite them to participate.
3. Providing them with a number they can call to opt-out of further contact.

Patients who do not choose to opt out of further contact will be called by a research assistant after two weeks and using a screening script, provided study details, screened for eligibility (i.e. AUDIT-C >0), and if potentially eligible, invited for a pretreatment assessment.

b, Flyers in the clinic: We will develop recruitment materials, similar to those we have used in earlier VA trials on alcohol with HIV-positive patients, for patients and providers. This will allow patients to call the study team directly (self-refer) and be referred by their providers.

c, Referral by providers: Providers can request permission to give a patient's name to study staff; or provide study information to patients in order for the patient to contact the study staff directly. Providers will be invited to refer patients they feel might be eligible for the study, using a script and information sheet (to be developed and submitted for approval at a future date).
As an aid to providers, study staff will review daily schedules and remind staff and providers to let patients who are likely to meet eligibility criteria (based upon review of medical records including previous labs, psychoactive medication that may interact with alcohol, AUDIT-C screening results and HIV status) know about the study. Providers will be given a reminder card regarding study eligibility criteria and the referral protocol.

d. In-person AUDIT-C: Patients presenting to clinic will be administered an AUDIT-C by research staff or in the context of routine clinical care. Those with an AUDIT-C>0 and potentially eligible will be invited for a pretreatment assessment.

b. Describe how potential subjects are contacted.

Potentially eligible patients will receive introductory letter about the study, a follow-up phone call to assess eligibility, and an invitation to meet with the research assistant (RA) to discuss the study on who will describe the study, determine interest in participating, and assess potential eligibility. In addition, we will develop recruitment materials, similar to those we have used in earlier VA trials on alcohol with HIV-infected patients, for patients and providers when patients present for HIV clinic appointments.

b. Who is recruiting potential subjects?

Research assistants and site investigators

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.
Potentially eligible patients who meet the inclusion criteria will be asked for written informed consent for screening and then asked to provide basic demographic and contact information, undergo indicated assessments, then including a PEth analysis. If the PEth is > 20 ng/ml they will be invited to complete written informed consent for study participation and enrolled in the study.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

☒ Names

☐ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☒ Telephone numbers

☐ Fax numbers

☒ E-mail addresses

☐ Social Security numbers

☒ Medical record numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☐ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web Universal Resource Locators (URLs)

☐ Internet Protocol (IP) address numbers

☐ Biometric identifiers, including finger and voice prints

☐ Full face photographic images and any comparable images

☐ Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects

☐ Yes, some of the subjects

☒ No

If yes, describe the nature of this relationship.

6. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment purposes

☐ For inclusion of non-English speaking subject if short form is being used

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

HIPAA Authorization waiver will be requested for initial patient screening and medical chart review, done only to inform subject eligibility. After patients have been identified as potentially eligibile, they will be invited to provide written informed consent for screening.

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   - ☒ Compound Consent and Authorization form
   - ☐ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.

   No patients will be seen at Yale and thus consent will not be obtained at Yale but only at the 7 participating sites: Atlanta GA, Bronx NY, Manhattan/Brooklyn NY, Dallas TX, Houston TX, Los Angeles CA, and Washington DC, New Orleans, LA.

9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

   All potentially eligible patients will be invited to provide written informed consent for screening. Then, all eligible patients will be asked for written consent for study participation using the Yale HIC approved Compound Consent and Authorization form by the site PI or the Research Assistant sessions and for permission to digital record their sessions with the Social Worker. Patients will be asked to come to a private office where they will meet with a Research Assistant or a PI who will describe the study in more detail. Patients will be given sufficient time to read through the consent form on their own. The PI or Research Assistant will then review the study and consent form with the patient and answer any questions. Once the patient is satisfied and has expressed his/her desire to continue with the study, s/he will be asked to sign and date the consent form as required. The

patient and PI or Research Assistant will sign and date the informed consent– one copy will go home with the patient; the original will remain in the patient's research chart.

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

    All research personnel are required to participate in and document training in protection of human subjects and the responsible conduct of scientific research, including assessment of a potential subject's capacity to consent to the study.

11. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

    Potential Participants will be given a Consent for Screening authorization form. Eligible individuals will be given Compound Consent and Authorization form with a detailed description of the purpose of the study, procedure, risks, benefits and rights to privacy/confidentiality to review and sign.

12. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use. **N/A**

    12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
    YES ☐ NO ☐

    Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

    Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

    If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

13. **Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study.** If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ **Not Requesting a consent waiver** ☐ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

Consent waiver will be requested for initial patient screening and medical chart review, done only to determine subject eligibility. After eligibility has been decided, written consent will be requested from all participating subjects.

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☒ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?
☒ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?
☒ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes, ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☒ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes No

☐ **Requesting a waiver of signed consent for the Entire Study (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:

a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. **Full waiver** of consent: (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for Recruitment/Screening only**

a. Does the research activity pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the <u>Entire Study</u> (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Prior to entrance into the study, each patient will have laboratory assessments CD4 lymphocyte count, HIV viral load, creatinine, platelets, hemoglobin, AST, ALT if not obtained in the past 60 days. In addition, HCV antibody and HCV viral load (if HCV antibody positive) will be obtained if not previously documented in patient's chart. Exhaled COtest or urine cotininewill be performed among patients who have smoked at least 100 cigarettes in their lifetime and who now report smoking cigarettes every day or some days. A urine pregnancy test will be performed on female subjects and must be negative prior to beginning the study medication and will be checked monthly. In addition, we will screen patients to exclude those who have a current diagnosis or are in remission for a gambling disorder. Demographic data to be will collected include age, gender, marital status, highest level education completed, employment, substance use history, duration of HIV disease, and a detailed HAART medication history. Charts will be extracted to collect health care information and service utilization information in the VA database, including labs, diagnoses, visits, medications, procedures, test results, and health care information and service utilization information in the VA database.

b. How will the research data be collected, recorded and stored?
c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☐ Laptop Computer ☐ Desktop Computer ☐ Other
d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

The Yale Center for Medical Informatics (YCMI) (http://ycmi.med.yale.edu/) will be responsible for data management using a web-based clinical trial management system (CTMS). Study data will be entered into the Web-accessible CTMS. To facilitate data monitoring the CTMS will generate web accessible reports and reminders to help monitor and manage the data collection process. The system can check for data inconsistencies, omissions, and errors regularly. Data questions or problems will trigger data queries and analyses of missing data will be done periodically to assure that all forms are entered and available for analysis.

Data Security is achieved via the following methods; 1) CTMS staff will receive HIPAA and Human Subjects Protection training, 2) Users will act in full compliance with HIPAA regulations, and 3) Sensitive data is encrypted. The web data-entry interface allows data entry from anywhere on the Internet and uses 128-bit secure sockets layer security to protect the confidentiality of the data. The CTMS also maintains an electronic audit trail of all modifications to study data. VA Connecticut houses and maintains the security and backup of all servers and workstations. Passwords and personal health information will be encrypted in the database server.

Data Transfer
Each recruitment site will consult with their local ISO and obtain a Sanctuary waiver as indicated by their local VA to connect the approved digital recorders to a VA PC. The digital recordings will be sent to a shared folder at West Haven VA and stored there. These files will be accessed by the coordinating center and members of the research team within the VA system.

Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Upon completion of the study, all computerized subject datasets will be de-identified and stored in a password-protected study computer, to which only the PI, investigators and study personnel will have access. All paper files with subject information will remain in locked files in the study office of the PI, until they are destroyed, after all analyses are complete.

Consistent with NIH policy, we are planning to make the results and accomplishments of the study available to the research community and to the public at large. We will adhere to the NIH Grants Policy on Sharing of Unique Research Resources including the "Sharing of Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Grants and Contracts" issued in December, 1999 http://ott.od.nih.gov/policy/rt_guide_final.html. Specifically, material transfers would be made with no more restrictive terms than in the Simple Letter Agreement or the Uniform Biological Materials Transfer Agreement and without read through requirements.

Following completion of the data collection and planned data analyses, we plan to publish the study results in scientific journals and to disseminate the findings in conferences and other appropriate forums. Final research data, consisting of the computerized dataset upon which accepted publications are based, and which do not contain any identifying personal health information, will be made available to other researchers on request and in some cases following

the acceptance for publication of the main findings from the final dataset. Documentation about the dataset, including information about the methodology and procedures used to collect the data, details about codes, definitions of variables, variable field locations, etc., will also be provided along with the final dataset. Even though the dataset will not include identifiers, there remains a remote possibility of deductive disclosure of subjects with unusual characteristics. Consequently, we will make the data and associated documentation available to users only under a data sharing agreement that provides for: 1) a commitment to using the data only for research purposes and not to identify any individual participant; 2) a commitment to securing the data using appropriate computer technology; 3) a commitment to refrain from disclosing or providing the data to other users; and 4) a commitment to destroying or returning the data after analyses are completed.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

During an audit or program evaluation, representatives from the Yale Human Investigation Committee and from the National Institutes of Health may have access to subject data, but will strictly follow rules of confidentiality

g. If appropriate, has a Certificate of Confidentiality been obtained? No

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

This protocol will include testing for hepatitis and therefore all positive test results will be reported to the patient's primary care physician for notification of the State Departments of Public Health in the states where the research sites are located, as mandated by law.

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

While there is no guaranteed benefit from participating in this study, participants in this study may benefit from counseling and medication which may lead to cessation or reduction in alcohol use and improvement in their ART medication adherence, improved HIV biological markers, and reduced HIV risk behaviors.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

Medications and counseling such as cognitive behavioral therapy, twelve-step facilitation and motivational interviewing have been found to be efficacious in the treatment of alcohol problems.
Individuals who are not eligible to participate or decline to participate may still receive treatment and other services to which they are otherwise entitled. All alcohol treatment medications are available at the medical centers participating in this study. Other non-medication treatments include counseling and referral to Alcoholics Anonymous or other support groups, which are also available.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

Contingency Management (CM) Rewards
CM visits will be provided by clinic Social Workers and will occur once every 3 weeks over 3 months (4 sessions). Rewards will be obtained through "draws" of paper slips from a bowl (fishbowl). The slips in the bowl will be set up in accordance with preset (See below) probabilities of rewards. At the VA sites, rewards will be provided as VA coupons in specific dollar amounts that can be used to purchase items at a VA Canteen store (similar to Walmart and Target stores). This strategy has been used successfully in CM programs in the VA.[33] At the beginning of treatment, the Social Worker will visit the local Canteen store with patients and have them identify items that they wish to purchase with their rewards. At the non-VA site, dollar amounts will be added to the reloadable ClinCard.

The bowl from which patients will draw will contain 100 slips of paper. Twenty slips will state "Good job" but not be associated with any tangible earnings. Sixty-four of the slips will state "$5", 15 will state "$25", and one will state "$100." Dollar amounts earned will relate to either coupons for use at the local VA Canteen store or be added to the ClinCard.

At each CM visit, patients will undergo a blood alcohol content analysis (BAC) with a breathalyzer or alcohol saliva test and provide a finger stick blood sample for PEth testing. The BAC/saliva test and PEth results will determine whether patients receive rewards for abstinence. Since PEth testing cannot take place onsite, PEth results will available within 72 hours.

Rewarding alcohol abstinence
Patients who provide a BAC or alcohol saliva test that is negative for alcohol (<0.003 g/dl) will get at least one opportunity to draw a slip of paper from the bowl and earn a monetary amount. The first draw may occur at the baseline visit to expose patients to the fishbowl. Whatever they earn from their BAC/saliva draw(s) ($5, $25 or $100) will be awarded immediately. They will earn at least one draw for each scheduled BAC/saliva that tests negative, and draws earned will escalate by one draw for each successive negative BAC/saliva test submitted. In total, patients can earn 14 draws for submitting negative BACs/saliva tests over the 12-week CM treatment phase.

If a patient's PEth test from an index visit is also negative (<8 ng/ml), he/she will also receive earnings. For the first PEth negative sample, patients will earn 5 draws, and the number of draws

earned will increase by one for each successive negative PEth sample provided. Although they will be awarded earnings immediately for the BAC negative samples, the PEth takes 3 days to process, and these actual earnings will be awarded when the PEth result becomes available. So long as the BAC tests negative, the patient will make their PEth draws at the in-person CM session (range 5-8 additional draws). Thus, patients will know that they will earn the amount drawn if the PEth is negative. If the PEth result is positive (>8 ng/ml), then the amounts from those draws will be forfeited (but the patient will still retain the amount earned from the draws for a negative BAC or saliva test). The Social Worker will notify the patient via telephone of the PEth result and amount being credited based on the value of the slip that was drawn at the CM session. In total, patients can earn up to 26 draws over the 3 months of CM if all 4 of their PEth readings are negative.

If a BAC or saliva tests >0.003 g/dl, then no draws will be awarded that day. The number of draws possible for the next negative BAC will reset to one, and the number of draws possible for the next PEth negative sample will reset to 5. After a reset, draws for both negative BACs/saliva tests and PEths will increase as before.

Rewarding addressing medical conditions impacted by alcohol and alcohol treatment goals
In addition to drawing slips for providing a negative BAC/saliva test and PEth, CM patients will also be able to earn drawings for demonstrating progress toward addressing a medical condition impacted by alcohol or completing specific activities related to attaining abstinence. One specific activity will be set at each visit with objective index of verification specified. The RA will verify these activities through VA EHR or documentation agreed upon in advance.[65,66] Patients will earn a minimum of 3 draws for each activity completed. Draws for completing activities will increase by one for each consecutive activity completed. If a patient fails to complete (or verify) an activity between visits, the number of draws earned will reset to 3 for the next week an activity is completed. These draws will be from the same bowl outlined earlier, and earnings will be awarded immediately upon verification of the activity. In total patients can earn up to 18 draws for completing 4 activities during the 3 months. In total, they can earn a maximum of 58 draws if they complete all 4 activities and submit all negative BACs/saliva tests and PEth, resulting in an average overall maximum of $461 in earnings, consistent with other successful 12-week CM protocols.[25,27,33,66]

Participant compensation for completing assessments
Participants will be compensated $50 completing each assessment at baseline assessment, during treatment (3 months), end of treatment (6 months) and the follow-up assessment at 9 and 12-months. The total possible compensation for completing study assessments is $250.

Participant compensation for travel to intervention visits
Each participant who is randomized to the CM plus stepped care group will receive $15 for each completed intervention visit.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

There are no costs to the subjects to participate in this research. At no cost to them, they will receive a medical evaluation including ongoing monitoring of their HIV markers, potentially receive medication to treat their heavy drinking, and will receive comprehensive psychosocial counseling addressing their drinking.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.

If a participant is injured as a direct result of participation in this study, treatment will be provided. The participant and/or his or her insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Participants will not waive their legal rights by participating in this study

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