STUDY PROTOCOL

CHOICE
Consider Healthier Drinking Options in Collaborative Care (CHOICE)

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I. Original Grant Submission Study Protocol
1) ABSTRACT

**Background:** Most patients with alcohol use disorders (AUD) never receive formal alcohol treatment, even those already engaged in primary care. Medical management of AUD in primary care settings, including repeated medically-focused brief interventions (BI), has proven effective for decreasing drinking. Monitoring abnormal laboratory tests may engage patients not initially interested in changing drinking, and medications can further improve outcomes among patients with alcohol dependence. However, implementing these evidence-based treatments will not occur by provider education alone—new systems of care delivery are required. The proposed randomized controlled trial tests a Collaborative Care intervention for delivering evidence-based care to AUD patients who do not respond to alcohol screening and BI. The VA is an optimal setting for an initial test of Collaborative Care for AUD because the VA has high rates of annual alcohol screening and clinical informatics systems required for Collaborative Care. **The Primary Aims** of the proposed trial are to determine whether primary care patients at high risk for current AUD who are offered Collaborative Care, compared to those randomized to usual care, (1) have fewer heavy drinking days and (2) are more likely to be abstinent or drinking below recommended limits without alcohol-related problems at 12 months follow-up.

**Methods.** This randomized controlled trial will enroll 300 adult VA primary care patients <65 years old (~200 men and 100 women) who are at high risk for current AUD based on their frequency of heavy drinking (> 5 drinks in a day for men and > 4 for women). Patients will be randomized to: 1) being offered Collaborative Care for AUD over 12 months or 2) usual care. The Collaborative Care Intervention consists of repeated scheduled visits for BI with a nurse care manager, as well as lab monitoring or medications for AUD when appropriate. The nurse care managers will be supported by a nurse practitioner and an interdisciplinary Collaborative Care Team. Main study outcomes include: 1) the number of heavy drinking days based on the Time Line Follow Back (TLFB), and 2) the proportion of patients who are abstinent or drinking below NIAAA recommended limits without alcohol-related problems based on the TLFB and Short Inventory of Problems (SIP), at 12 months. Generalized estimating equations, adjusted for appropriate covariates, will compare groups based on intention to treat. Secondary outcomes include process measures of treatment engagement, secondary drinking measures, resolution of abnormal lab markers, and inpatient health care utilization. Impact. Broad agreement exists that new approaches for delivering care to patients with AUD are needed, including offering evidence-based care within medical settings. This study, proposed by a New NIH investigator and a team of experts in collaborative care and addictions treatment, tests a system of care delivery proven effective for other mental health conditions. The study team has extensive success designing, testing, and implementing systems for alcohol screening and BI nationwide in VA and conducting clinical trials for AUD, which will inform the proposed study.
SPECIFIC AIMS

Alcohol use disorders are common and often chronic and relapsing conditions, which are associated with substantial morbidity, mortality, and cost. Although specialty treatment improves outcomes and decreases health care costs for patients with alcohol use disorders, most patients with alcohol use disorders never receive treatment. Even in the uncommon occurrence that health care providers refer patients with alcohol use disorders to alcohol treatment, most do not go.

Two types of evidence-based care for alcohol use disorders could be offered in primary care and are outlined in the 2007 NIAAA Clinicians Guide. First, repeated brief interventions reduce drinking. Second, FDA-approved medications for alcohol dependence, combined with medical management, improve drinking outcomes.

What is not known is how to integrate evidence-based practices in an organized way into primary care settings. The Chronic Care Model is a proven approach for organizing systems of care for chronic conditions. Collaborative care interventions, based on the Chronic Care Model, are effective for delivery of evidence-based primary care for depression. However, to our knowledge, collaborative care has not been tested for management of alcohol use disorders in primary care. Collaborative care could increase engagement of primary care patients with alcohol use disorders in evidence-based alcohol-related care, and thereby improve drinking outcomes.

The proposed study will evaluate the effectiveness of a collaborative care intervention for evidence-based management of alcohol use disorders in primary care settings. The study is led by a New NIH Investigator but brings together an experienced team of VA and NIH investigators. The study will be conducted in the VA because the VA has the infrastructure, clinical information systems, and “system readiness” required for collaborative care for alcohol use disorders. The long-term purpose of the proposed research is to identify an effective system for delivery of evidence-based care for alcohol use disorders to primary care patients.

The proposed study is a randomized controlled effectiveness trial of collaborative care for alcohol use disorders. The Collaborative Care intervention is a care delivery system designed to engage primary care patients in evidence-based care for alcohol use disorders. The study will test Collaborative Care for alcohol use disorders in 300 adult patients less than 65 years old who are actively engaged in primary care in the VA (including ~100 women).

a) The Primary Aim is to determine whether primary care patients at high risk for alcohol use disorders who are offered Collaborative Care have improved drinking outcomes compared to those who are offered Usual Care. We will specifically test whether patients offered Collaborative Care:

1. Have fewer heavy drinking days at 12 months follow-up; and
2. Are more likely to be abstinent or drinking below recommended limits without problems at 12 months follow-up.

b) Secondary Aims

We will complete secondary analyses to:

1) Compare patients randomized to Collaborative Care and Usual Care with regard to:
   a) engagement in care for alcohol use disorders;
   b) secondary drinking outcomes (e.g. heavy drinking days at 3 months);
   c) changes in laboratory markers of heavy drinking;
   d) health-related quality of life; and
   e) health care utilization and costs over 12 months follow-up; and
2) Estimate the costs of the intervention.
3) BACKGROUND AND SIGNIFICANCE

The Need for New Approaches to Treating Alcohol Use Disorders (AUD)

Alcohol use disorders are common and often chronic.\textsuperscript{1-3} About 8.5% of the US population meets Diagnostic and Statistical Manual of Mental Disorders, 4\textsuperscript{th} edition (DSM-IV) criteria for current alcohol use disorders (AUD),\textsuperscript{4, 5} and the lifetime prevalence is 30.3%.\textsuperscript{6} Current DSM-IV AUD are most common in young adults with a prevalence of 10.8% among 18-29 year olds.\textsuperscript{5} The prevalence is also higher in patients with other psychiatric conditions.\textsuperscript{7} While many patients resolve AUD without treatment, the majority do not. Among individuals interviewed for the National Epidemiologic Study of Alcohol and Related Conditions (NESARC) who met diagnostic criteria for DSM-IV alcohol dependence prior to the past year, almost two-thirds continued to drink at unhealthy levels and/or experience symptoms of dependence.\textsuperscript{8}

Alcohol use disorders appear to be on a single continuum. There is increasing recognition of alcohol dependence as a single continuum. The continuum of alcohol dependence includes symptoms considered “abuse” based on DSM-IV, as well as alcohol consumption.\textsuperscript{9-11} Based on accumulating evidence,\textsuperscript{12, 13} a recent review concluded that DSM-IV abuse and dependence “are not distinct categories” and that the abuse category should be abandoned in the fifth edition of the DSM, with substance dependence defined by a single set of criteria.\textsuperscript{9}

Definitions. In this proposal, we will use alcohol use disorders (AUD) to refer to this continuum from abuse to dependence, reserving the term alcohol dependence for DSM-IV alcohol dependence. We use heavy drinking to refer to drinking above NIAAA daily limits (drinking 5 or more drinks in a day for men and 4 or more drinks for women). We use risky drinking to refer to drinking above daily or weekly limits recommended by NIAAA (daily limits above and weekly limits defined as 14 drinks a week for men and 7 for women).\textsuperscript{14} Finally, unhealthy drinking is used to describe the entire spectrum from risky drinking to severe dependence.\textsuperscript{15}

Frequent heavy drinking is strongly associated with AUD. Heavy drinking is part of the alcohol dependence continuum, and the frequency of heavy drinking reflects the severity of dependence.\textsuperscript{16} Weekly heavy drinking is associated with mild dependence and daily heavy drinking is associated with more severe symptoms.\textsuperscript{12, 13} Several experts have suggested that heavy drinking twice a week or more often should be included in criteria for alcohol dependence in DSM-V.\textsuperscript{9, 10} Therefore, assessing the frequency of heavy drinking is a relatively easy approach to identifying patients at high risk for AUD.

Most individuals with AUD never receive needed treatment. Although specialty addictions treatment of AUD improves outcomes\textsuperscript{17, 18} and decreases health care costs,\textsuperscript{19, 20} the majority of patients with AUD do not receive treatment.\textsuperscript{6} Eighty-five percent of people with lifetime AUD never receive any alcohol treatment.\textsuperscript{6} Even among patients identified within medical care settings, only 11% of patients with alcohol dependence are referred for specialty treatment,\textsuperscript{21} which has been noted to be “a greater discrepancy between care actually delivered and recommended care”, than for any other area of health care.\textsuperscript{22}

Efforts to refer patients to alcohol treatment are often unsuccessful. When medical providers do refer patients to alcohol treatment, patients often do not go. Thirty-six percent of inpatients\textsuperscript{23, 24} and 90% of primary care and ED patients\textsuperscript{25, 26} referred to alcohol treatment do not follow through with the referral. NESARC participants who met criteria for lifetime AUD reported a number of reasons for not seeking help for their drinking (Table 1).\textsuperscript{6} These findings are consistent with previous research on barriers to treatment.\textsuperscript{22, 27-35}
Formal alcohol treatment is not acceptable to many patients with AUD.\textsuperscript{36, 37} Among the 15% of NESARC participants with a lifetime diagnosis of AUD who ever sought help related to their drinking, most attended 12-step programs such as Alcoholics Anonymous (AA), and less than half reported formal alcohol treatment (Table 2).\textsuperscript{6} Individuals who do receive formal treatment often have more severe drinking problems than those who do not, which may account for the focus on total abstinence in these programs.\textsuperscript{36} Based on this pattern, one leading addictions researcher concluded that “the unfortunate side effect is that … a very large proportion of individuals who could benefit from reductions in their heavy drinking” consider abstinence-oriented treatment “extreme and undesirable.”\textsuperscript{36}

There is widespread agreement that new models of care are needed for AUD.\textsuperscript{36, 38} The Institute of Medicine (IOM) called for a broadening of the base of alcohol treatment almost 20 years ago.\textsuperscript{39} More recently, the IOM articulated the inability of current systems of care to improve health care for chronic conditions and called for a fundamental redesign of systems of care.\textsuperscript{40, 41} In 2005, the President’s New Freedom Commission on Mental Health recommended individualized care plans, shared decision-making, offering combinations of evidence-based practices, and using information systems to improve access and coordination of care.\textsuperscript{42, 43} Leaders in addictions care are now calling for new models of care that are consistent with these recommendations.\textsuperscript{37, 44, 45} NIAAA has recommended that medical providers, and primary care providers in particular, are ideally situated to address the treatment gap for AUD.\textsuperscript{14, 38}

Table 1. Reasons for not seeking help for drinking*

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should be strong enough to handle it on own</td>
<td>44%</td>
</tr>
<tr>
<td>Did not need help</td>
<td>32%</td>
</tr>
<tr>
<td>Too embarrassed to discuss it with anyone</td>
<td>18%</td>
</tr>
<tr>
<td>Did not want to answer questions</td>
<td>10.3%</td>
</tr>
<tr>
<td>Financial barriers</td>
<td>12.7%</td>
</tr>
<tr>
<td>Not wanting to “go to treatment”</td>
<td>11.2%</td>
</tr>
<tr>
<td>Not thinking treatment could help</td>
<td>8.4%</td>
</tr>
<tr>
<td>Not knowing where to seek help</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

* In NESARC participants with lifetime DSM-IV alcohol use disorders

Table 2. Settings Where People w/ AUD Sought Help

<table>
<thead>
<tr>
<th>Setting</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-step programs (e.g. AA)</td>
<td>76%</td>
</tr>
<tr>
<td>Alcohol or drug rehab program</td>
<td>45%</td>
</tr>
<tr>
<td>Physicians, psychologists or social workers</td>
<td>37%</td>
</tr>
<tr>
<td>Outpatient clinics</td>
<td>29%</td>
</tr>
<tr>
<td>Emergency Departments</td>
<td>26%</td>
</tr>
</tbody>
</table>

Evidence-Based Care for Primary Care Patients with AUD

Alcohol screening and brief intervention (BI) reduce drinking among primary care patients with unhealthy alcohol use.\textsuperscript{46, 47} Population-based alcohol screening followed by BI has been designated the 3\textsuperscript{rd} highest prevention priority for US adults, after smoking cessation counseling and aspirin for prevention of heart disease.\textsuperscript{48, 49} Efficacious BIs typically include feedback linking drinking to health and advice to cut down or abstain, as well as agreement on a drinking goal.\textsuperscript{50-52} Whereas single session BIs have small effects (0.19),\textsuperscript{53} repeated BIs have significantly greater benefits (effect sizes 0.47-0.61).\textsuperscript{53}

The efficacy of BIs for alcohol dependence is debated. Because 74-79% of trials testing the efficacy of BI have excluded patients with alcohol dependence,\textsuperscript{54} information on the efficacy of BI for alcohol dependence is incomplete. Some experts have concluded that BI does not reduce drinking in patients with alcohol dependence.
dependence, while others have noted that trials of BI that included alcohol dependent patients have had the largest effect sizes.\textsuperscript{23-26, 54, 56}

However, \textit{repeated} BIs are clearly effective for patients with AUD. Despite the debate about the efficacy of BI for alcohol dependence, there is increasing evidence for the efficacy of \textit{repeated} BIs for patients with AUD. Several studies have supported the willingness of alcohol dependent patients to engage in repeated BIs\textsuperscript{54, 57, 58} and confirmed the benefits for patients with AUD who engage.\textsuperscript{59} Several types of repeated BI have been evaluated and are described below. They include telephone assessment and feedback; monitoring abnormal alcohol-related labs; and medical management with placebo.

\textbf{a. Repeated BIs over the telephone are effective for reducing drinking in patients with AUD.}\textsuperscript{57, 59} A randomized controlled trial of 3-6 telephone-based brief intervention sessions with patients with AUD demonstrated a significant decrease in drinking at follow-up among male intervention patients at 3 months (p=0.001).\textsuperscript{57} This effect was demonstrated in spite of the fact that the intervention was stopped after the 3\textsuperscript{rd} session for about 50% of patients in the intervention group who were not interested in decreasing their drinking. Patients who engaged in 6 telephone calls reported drinking significantly more at baseline than those who engaged in fewer visits. Although women in this trial also had decreased drinking, decreases were not significantly different in the intervention and control arms.\textsuperscript{57} The investigators attributed these negative findings to the reactivity of research assessments and urged future studies to “use entry criteria based on the amount of alcohol consumption and avoid administering extensive baseline interviews.”\textsuperscript{57} Such reactivity, which has been thoroughly demonstrated recently,\textsuperscript{46, 60-62} likely reflects several mechanisms: regression to the mean, social desirability bias, or true changes in drinking due to increased awareness of drinking.\textsuperscript{63}

\textbf{b. Repeated BI with feedback regarding abnormal alcohol-related laboratory tests.} Whereas the repeated telephone trial above terminated after 3 visits if patients were not interested in changing, other repeated interventions have been used to engage patients in alcohol-related discussions irrespective of their readiness to change. These trials use repeated BI for monitoring of abnormal alcohol-related lab tests.\textsuperscript{64, 65} Willenbring and Olson recruited inpatients who were hospitalized for medical problems due to drinking and were not ready for abstinence-oriented alcohol treatment but were willing to attend monthly primary care visits with a nurse practitioner to monitor their medical problems. Patients randomized to the intervention were invited to attend monthly visits for monitoring labs (e.g. gamma glutamyl transferase; GGT) or other biomarker (e.g. blood pressure), and were nearly twice as likely as patients randomized to usual care to report abstinence at 2 years (74\% vs 47\%; p =0.02).\textsuperscript{66} Recently, lab monitoring with carbohydrate deficient transferrin (CDT) has been found efficacious for reducing drinking in primary care samples.\textsuperscript{67} A negative trial only offered lab feedback on 2 occasions and measured outcomes over 6 months later.\textsuperscript{68} Lab monitoring has also been shown to be associated with large changes in drinking in a cohort study of patients with alcohol dependence (mean decreases from 16 to 2.5 drinks per day on average).\textsuperscript{59} Repeated feedback on other objective markers of heavy drinking (e.g. blood pressure) is also effective.\textsuperscript{66, 70}
Medical management (MM) and placebo pills decreased drinking among alcohol dependent patients. The COMBINE trial of naltrexone and acamprosate tested medical management (MM; Table 3) and placebo pills as one of 9 trial arms. The MM and placebo intervention was as efficacious as a state-of-the-art combined behavioral intervention, and, at low “willingness to pay” thresholds, more cost effective than the combination of MM and active medications. The 4-month MM intervention (Table 3) was designed to be compatible with primary care and appeared most efficacious when it was delivered in a flexible manner. Specialty behavioral treatments, such as motivational interviewing, were not included in the MM intervention to increase generalizability. Although labs were checked once halfway through the trial if GGT was abnormal at baseline, lab monitoring was not a central part of the protocol.

FDA-approved medications for alcohol dependence. Three FDA-approved medications for alcohol dependence are currently recommended by the NIAAA for use in medical settings. Disulfiram, commonly known as Antabuse®, is the oldest FDA-approved medication for alcohol dependence. Disulfiram causes an aversive reaction (flushing, nausea, vomiting) if patients drink alcohol. Supervised daily administration of disulfiram (250 mg) has proven efficacy for alcohol dependence based on meta-analyses (Table 4) with a moderate effect size of 0.53. In a VA trial of disulfiram, subjects taking 250 mg per day did not have higher total abstinence rates over 12 months compared to those taking 1 mg disulfiram per day or those taking a vitamin pill. However, among study completers, those on 250 mg disulfiram per day had significantly fewer drinking days than those in the other two conditions.

Naltrexone is an opiate antagonist, available orally or via monthly injections, shown to decrease drinking and craving. A recent review of all double-blind trials of naltrexone from 1990-2006 revealed that studies that evaluated whether naltrexone decreased measures of “any drinking” were less likely to show a benefit (36%) compared with those that evaluated whether naltrexone decreased heavy or excessive drinking (70%). A VA trial focused on abstinence initially found no benefit of naltrexone, but results of a more statistically robust re-analysis showed that naltrexone was efficacious in patients with abstaining or sporadic (vs. consistent) drinking trajectories and that the original negative results were likely a reflection of the high rate of abstinence in both groups (intervention and control) among the motivated patients recruited for the trial. When combined with 9 sessions of MM over 16 weeks, naltrexone was associated with improved drinking outcomes compared to MM and placebo. Maximizing adherence is important in effectively implementing naltrexone, and offering psychosocial support may improve its efficacy. Acamprosate is a glutamate modulator that appears to reduce alcohol craving, although the exact mechanism for decreasing drinking is unknown. Although no more efficacious than medical management (MM) and placebo in the recent COMBINE trial, acamprosate compared to placebo increased total abstinence rates in several European trials in which the subjects had established abstinence prior to
randomization in the trial. A recent meta-analysis summarized the literature on these three medications (Table 4). \(^5\)

Several ongoing studies are evaluating the efficacy of individual medications, \(^82, 84\) or conducting adaptive trials of series of treatments \(^65\) and new medications for alcohol dependence are on the horizon. \(^86-88\) The National Institute for Alcohol Abuse and Alcoholism (NIAAA) recommends combinations of these evidence-based practices for patients with AUD. \(^4\) However, to our knowledge, no study is evaluating how to offer all these evidence-based practices—repeated BI with or without lab monitoring and medications for dependence—to primary care patients with alcohol use disorders.

**Need for Systems to Implement Evidence-based Treatment for AUD into Primary Care**

**Beyond provider education.** Over the past decade, led by the IOM, efforts to improve the quality of US health care have moved from a focus on provider education alone to broader systems redesign. \(^40\) Although provider education, training, or academic detailing can improve primary care providers’ skills, \(^89-93\) provider education is seldom sufficient to improve the quality of health care. \(^94\) Improved management of AUD in primary care is not expected to be any different. \(^95, 96\) Thus, despite the known efficacy of primary-care based treatments and expert recommendations for incorporating these practices into routine care, improving the quality of primary care for AUD will require organized systems to ensure the delivery of evidence-based care.

**Wagner’s Chronic Care Model.** The Chronic Care Model is a proven framework for improvements in care for chronic diseases. \(^97\) The Chronic Care Model of quality improvement is built on evidence that, in addition to increasing provider expertise and skill, 3 types of changes in practice lead to the greatest improvement in health outcomes: educating and supporting patients; making care delivery more planned and team-based; and making better use of information systems for population-based identification of high-risk patients, decision support, and communication. \(^98\) The model also emphasizes linking patients to community resources to support patient self-management. Together these components result in an activated informed patient and a prepared pro-active care team.

**Proven effectiveness of the Chronic Care Model.** The Chronic Care Model has been widely adapted and proven effective for management of depression in primary care settings. \(^98, 99\) The Chronic Care Model has also been endorsed by the IOM for evidence-based improvement of quality of care. \(^40\) A meta-analysis of studies evaluating Chronic Care Models for quality improvement found that organizing care for patients with chronic illnesses based on the Chronic Care Model improved processes of care and clinical outcomes. \(^100\) In addition, implementation of the Chronic Care Model in primary care settings provides a substantial cost benefit. \(^100-102\)

**Applying the Chronic Care Model to AUD.** The Chronic Care Model has been proposed for improving preventive care for unhealthy drinking and linkage of patients to treatment for AUD. \(^103, 104\) A recent study found that health care practices with systems consistent with the Chronic Care Model were more likely to offer preventive care for risky health behaviors, including unhealthy drinking. \(^105\) An ongoing NIAAA-funded study \(^106\) is evaluating whether the Chronic Care Model can improve care for alcohol dependent patients recruited from detoxification units into a primary care clinic. \(^104\) To our knowledge, no study has evaluated reorganization of care for patients with AUD who are already participating in primary care.

**Summary of Background.** Alcohol use disorders are common and result in substantial morbidity. Although specialty treatment can help, most patients with alcohol use disorders never receive formal alcohol treatment. Two types of evidence-based treatments could be provided for patients with AUD in primary care and are recommended in the NIAAA Clinicians Guide: 1) repeated brief interventions incorporating lab
monitoring as appropriate, and 2) medications for patients with alcohol dependence. However, results of quality improvement research are clear: new systems of care delivery are needed to deliver evidence-based care to primary care patients with alcohol use disorders. Wagner’s Chronic Care Model provides a strong foundation for development of such systems. Such a model would include population-based screening, proactive assessment of high-risk patients, planned care organized to be acceptable to patients and provided by an interdisciplinary team, and a clinical informatics structure to support screening, decision-support and communication. Although many leaders have called for new systems of delivery for care to patients with AUD, no study has tested such a model of care for patients with AUD who are engaged in primary care and identified by population-based screening.

RESEARCH DESIGN AND METHODS

Overview. The proposed randomized controlled encouragement trial will evaluate the effectiveness of a Collaborative Care (CC) delivery system for the management of AUD in primary care. The CC intervention is designed to engage primary care patients with AUD in patient-centered and proactive evidence-based care for AUD (Table 9). We hypothesize that primary care patients at high risk for AUD, who are offered the CC intervention, will decrease their frequency of heavy drinking and be more likely to be abstinent or drinking below recommended limits without problems at 12 months follow-up.

Subjects: Primary care patients less than 65 years old from a 2-site VA facility will be eligible if they are at high risk for current AUD based on AUDIT-C alcohol screening scores ≥ 5 and self-report of recent frequent heavy drinking. Randomization: Three hundred patients (estimated 100 women and 200 men) will be randomized to the CC intervention or Usual Care stratified by: gender; the presence of any abnormal alcohol-related laboratory marker (GGT, CDT, or mean corpuscular volume [MCV]) at baseline; and the presence of past-year DSM-IV alcohol dependence at baseline. Intervention: Patients randomized to CC will be offered evidence-based care over 12 months via a CC delivery system whereas patients randomized to Usual Care will not be offered any additional care. The CC intervention consists of scheduled visits with a registered nurse care manager (CC nurse), with support from a nurse practitioner (NP) for medications for alcohol dependence or withdrawal management. Both the CC nurse and NP will consult with an interdisciplinary CC Team and patients’ providers. The goal of the intervention is to engage patients in evidence-based medical management of AUD: repeated BI within a medical context based on COMBINE trials’ Medical Management (MM) adapted for patients who may not be: alcoholic dependent; ready to consider abstinence; open to medications; willing to try mutual help groups.

Main study outcomes include: 1) the number of heavy drinking days in the past four weeks, and 2) abstinence or drinking below recommended limits without problems at 12 months. Main analyses will be conducted based on intention to treat (e.g. by treatment assignment). Secondary analyses compare CC and Usual Care groups with regards to process measures of engagement in alcohol-related care, secondary drinking outcomes, changes in laboratory markers of heavy drinking, health-related quality of life, health care utilization, and health care costs. Additional secondary analyses evaluate the cost of the intervention.

Table 5. Evidence-based AUD Care that will be Offered Via CC

<table>
<thead>
<tr>
<th>CC for AUD is designed to engage patients with AUD in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Repeated BI within a medical context based on COMBINE trials’ Medical Management (MM) adapted for patients who may not be:</td>
</tr>
<tr>
<td>• alcohol dependent</td>
</tr>
<tr>
<td>• ready to consider abstinence</td>
</tr>
<tr>
<td>• open to medications</td>
</tr>
<tr>
<td>• willing to try mutual help groups</td>
</tr>
<tr>
<td>2. Monthly monitoring of alcohol-related labs or BP, if abnormal at baseline</td>
</tr>
<tr>
<td>3. Medications for DSM-IV alcohol dependence, as appropriate</td>
</tr>
</tbody>
</table>
STUDY SETTING AND SAMPLE

VA Puget Sound Primary Care Clinics. The VA was selected as the site for this study based on its clinical informatics system, population-based alcohol screening, and clinical need. VA Puget Sound is a multisite facility that in fiscal year 2008 cared for 34,703 primary care patients in 4 clinics at 2 locations, Seattle and American Lake, in Tacoma, Washington.

Study sample. This study will enroll 300 patients at high risk for AUD over 2.5 years (10 quarters; 130 weeks), with an average of 2.3 patients a week. Inclusion criteria are shown in Table 10. Adults less than 65 years old who screen positive on the AUDIT-C (> 5 points) will be eligible if they are at high risk for AUD based on a Brief Telephone Screen. Inclusion criteria are designed to be practical for primary care follow-up of patients after alcohol screening and BI, and use the frequency of heavy drinking to identify patients at high risk for AUD.\textsuperscript{14, 164-166} The frequency of heavy drinking is strongly associated with symptoms of DSM-IV dependence\textsuperscript{12, 13, 16} and may be included in DSM-V criteria for alcohol dependence.\textsuperscript{9, 12, 13} Older adults are excluded in order to focus on patients known to benefit from medications for alcohol dependence and repeated telephone BI.\textsuperscript{57}

### Table 6. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. AUDIT-C score 5 or more;</td>
</tr>
<tr>
<td>2. Age less than 65 years at the time of AUDIT-C screening;</td>
</tr>
<tr>
<td>3. Frequent Heavy Drinking based on patient report at Brief Telephone Screen, including at least:</td>
</tr>
<tr>
<td>- 8 heavy drinking days in the past four weeks (&gt; 5 drinks in a day for men; &gt; 4 women) OR</td>
</tr>
<tr>
<td>- 4 heavy drinking days in the past four weeks and documentation of prior alcohol treatment or attendance at AA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Missing address or phone in VA’s Computerized Patient Record System (CPRS)</td>
</tr>
<tr>
<td>2. Warning flag regarding violent behavior in CPRS</td>
</tr>
<tr>
<td>3. Patient participating in addictions treatment (VA or non-VA)</td>
</tr>
<tr>
<td>4. Primary care provider or patient indicates not to contact patient</td>
</tr>
<tr>
<td>5. Barriers to telephone assessment: hearing problem; non-English speaking</td>
</tr>
<tr>
<td>6. Unable to provide adequate collateral contacts</td>
</tr>
<tr>
<td>7. Cognitive impairment based on MINICOG &lt; 3</td>
</tr>
<tr>
<td>8. Unstable or acute medical, surgical or psychiatric problem requiring emergent treatment</td>
</tr>
<tr>
<td>9. Not available for follow-up: planning to move within year; life expectancy &lt; 1 year; enrolled in hospice</td>
</tr>
<tr>
<td>10. Pregnancy</td>
</tr>
</tbody>
</table>

Overview of recruitment. The proposed effectiveness trial is intended to evaluate CC for AUD in a “real-world” setting as much as possible within the context of a randomized controlled trial and to minimize assessment reactivity.\textsuperscript{46, 57, 62, 63} Therefore, we will not conduct diagnostic interviews to establish eligibility and there will be relatively few exclusions. The study uses a three-step process of recruitment (Figure 3), which is detailed below. As an overview, in Step 1 electronic data will be used to identify patients in the eligible age group who screen positive on the AUDIT-C (≥ 5). In Step 2 potentially eligible patients will be called for a Brief Telephone Screen that identifies patients at high risk for AUD based on the frequency of heavy drinking and prior alcohol treatment. In Step 3 eligible patients will be consented and enrolled, followed by an in-person Baseline Research Assessment and a telephone survey before randomization.

Step 1. Electronic Identification of Patients at High Risk for AUD. Patients at high risk for AUD will be identified using weekly queries of VA’s Computerized Patient Record System (CPRS) for results of routine
clinical AUDIT-C screening and age. Only patients with both an address and phone number in CPRS will be eligible. If providers give permission to contact patients, potentially eligible patients will be sent introductory letters, with an enclosed $2 bill as an incentive, inviting them to participate in a study of patients' drinking over time in which some patients will be offered medical support to help decrease drinking, including medications and monitoring special labs. The letter indicates that participants will be compensated $10 for an in-depth baseline assessment, $15 for a 20-minute telephone assessment at 3 months, and $25 for the 12-month assessment ($10 for scheduling and $15 for completing the assessment). If they prefer not to be called, patients will be allowed to “opt-out” via addressed, stamped postcard, email, or calling a toll-free 800 number.

No Contact Group of Men. Because many more men will be eligible than are needed for the study, we will randomly sample men for recruitment, resulting in a random “no contact group” of men who were otherwise eligible based on electronic screening of age and AUDIT-C score. This no contact group will be used in secondary analyses of a potential “reactivity effect” of the recruitment procedure. This no contact group will consist initially of 25% of potentially eligible men but may be adjusted over time if we exceed our recruitment targets for men.

Step 2. Brief Telephone Screen. Patients who do not “opt out” will be telephoned for the Brief Telephone Screen. The screening protocol is designed to be brief and unobtrusive in order to have minimal reactivity effects. The Brief Telephone Screen will use 3 questions to assess the frequency of heavy drinking and any history of alcohol treatment or attending AA for a drinking problem (see Data Collection below) and will also identify patients currently in alcohol treatment for exclusion. Patients will also be asked their racial and/or ethnic background. For ethical reasons, given the proven efficacy of BI and requirements for BI in VA, all patients screened by telephone who do not have BI documented after their positive AUDIT-C will be offered a standard BI which will include: 1) advice to drink within recommended limits and 2) general feedback that drinking above those limits can impact their health.
Figure 3. Overview of Proposed Collaborative Care Trial to Increase Evidence-based Management of Primary Care Patients with AUD

1a. Identify High-risk Patients Electronically
- AUDIT-C ≥ 5 and < 65 years old

1b. Permission to contact
Provider indicates OK to contact patient → patient sent letter

2. Brief Telephone Screen
- Telephone verbal consent: 5-10 min. interview
- Eligibility Screen:
  - 8 HDD/28 days OR 4 HDD/28 days AND prior Tx
  - Interested in study of drinking over time: paid for assessments; patients will be told some patients will be offered medications, special labs
  - No exclusion criteria

Eligible and interested

3. In-person Baseline Research Assessment (~N 380)
- Written Informed Consent
- Meets inclusion and no exclusion criteria
- Estimated 300 eligible: 100 women & 200 men

Randomization*
(N 300)

Usual Care
Continued primary care, mental health, and addictions treatment referral as usual

Collaborative Care (CC)
Continued Usual Care PLUS offered Collaborative Care

Engagement in Care for Alcohol Dependence

Drinking Outcomes at 12 Months
Aim 1: Number of heavy drinking days past 4 weeks
Aim 2: Abstinent or drinking < recommended limits w/o problems past 4 weeks

Exclusions:
Step 1 – CPRS*
- No contact info
- Violence warning flag
- In addictions treatment

Step 2 - Brief Telephone Screen
- Barriers to assessment: cognitively impaired, intoxication, etc.
- Barriers to telephone: deaf, language, etc.

Step 3 – Baseline Assessment
- Do not complete labs or telephone survey
- Acute medical problem: suicidal, emergent medical condition; etc.
- Not available at 12 months: moving, expect incarceration, hospice
- Inadequate contacts

* LEGEND: Stratified by gender, +/- abnormal lab, and +/- DSM-IV alcohol dependence; heavy drinking days defined as ≥ 5 drinks men and ≥ 4 women; Computerized Patient Record System (CPRS) is VAs electronic medical record
Intervention and Usual Care Conditions

Randomization. Following the written informed consent process and all required baseline assessments, eligible patients who consent will be randomly assigned to either the Collaborative Care (CC) intervention or the Usual Care control group. The unit of randomization is the individual patient. Patients will be randomly assigned to CC or Usual Care in approximately equal numbers, and randomization will be stratified by gender, DSM-IV alcohol dependence, and whether or not patients had any abnormal alcohol biomarker at baseline (GGT, CDT or MCV). We stratify to ensure balanced groups for evaluating effect modification by each stratification variable, expecting ~33% women, ~50% alcohol dependent, and ~30% of patients with one or more abnormal alcohol biomarkers.

Within the 8 strata based on the 3 stratification variables, patients will be randomized in permuted (variable) blocks of 6, 8, and 10 patients. Randomly varying block sizes minimizes the ability of study personnel to anticipate assignment of the last patient in each block. The sequence of each block will be predetermined at random and kept in sealed envelopes prepared prior to recruitment. Patients will be told that they are agreeing to a study of changes in drinking over time that will require follow-up telephone surveys of all patients at 3 and 12 months and labs at 12 months, and that some patients will be offered additional care. After patients consent to enroll in the trial the Project Director will open a randomization envelope for enrolled patients. After the baseline assessment and randomization, except for blinded telephone surveys to assess outcomes at 3 and 12 months by an independent Survey Research Program (SRP), patients randomized to the Usual Care group will be not be contacted by study staff.

Collaborative Care (CC) Intervention. The Collaborative Care (CC) intervention is a team-based delivery system for evidence-based primary care for AUD (Figure 4). The evidence-based primary care that will be delivered via CC is a flexible adaptation of the COMBINE trial’s medical management (MM) protocol and other primary care trials reviewed above and is consistent with the NIAAA Clinician’s Guide (2007 revision). Adaptations to MM are necessary for CC management of AUD because identification of patients with population-based screening will identify some patients who are uninterested in changing their drinking. Further, only some patients will meet diagnostic criteria for alcohol dependence, and many may be unwilling initially to consider abstinence as a goal, to attend AA, or try medications for alcohol dependence. Therefore, the intervention will include repeated BI by a CC nurse, with or without lab monitoring, as indicated, to engage patients in alcohol-related medical care. Care will be centered on patient’s goals for change based on evidence that matching patients’ care to their preferences improves outcomes and findings in COMBINE that clinician flexibility was associated with improved outcomes.
Engaging patients - the core of Collaborative Care (CC) for AUD. Engaging patients in scheduled visits to address drinking—by telephone or in-person—is at the core of the CC intervention. CC patients will have repeated, planned visits with a registered nurse care manager (CC nurse) to address drinking and provide BI consistent with the MM protocol (Table 3), along with lab monitoring and medications for alcohol dependence when appropriate (Table 9). If patients are not ready to change their drinking, repeated feedback, as in the trial of repeated BI over the telephone, will be used with objective lab or other medical feedback (e.g. blood pressure), if applicable. Pharmacologic management will focus on FDA-approved medications currently recommended by the NIAAA Clinicians Guide\textsuperscript{14} and available in VA, although recent and ongoing trials suggest others are also efficacious\textsuperscript{86-88} and may eventually be appropriate for widespread use.\textsuperscript{38} The initial visit with the CC nurse will include review of alcohol consumption and components of the Baseline Assessment (see Table 12), and all assessments and visits will be documented in progress notes in the VA Computerized Patient Record System (CPRS). CC nurse visits (telephone or in-person per patient preference) will occur weekly for 1 month, biweekly for 1 month, and monthly thereafter for 10 months.

After the initial visit with the CC nurse, all CC patients will be evaluated by a nurse practitioner (NP). Although we initially hoped to have primary care providers write prescriptions for recommended medications for alcohol dependence, our preliminary qualitative findings from discussions with providers, has convinced us that a majority of primary care providers would not be comfortable initiating medications for alcohol dependence or managing withdrawal on an outpatient basis, even with consultation available from a CC team and management by a care manager. Therefore, an NP is included on the CC team and will see all patients at baseline and when medications are changed, recommending and initiating medications as indicated, and managing alcohol withdrawal as necessary with CC nurse support.

Collaborative Care (CC) Team. Both the CC nurse and the NP will participate in and be supported by an interdisciplinary CC Team. In addition to the CC nurse and NP, the CC Team will include addictions psychiatrists with expertise in use of alcohol dependence medications and withdrawal management (AS and JR),\textsuperscript{160, 173-178} 2 behavioral health experts with expertise in BI trials and CC (EL and DG),\textsuperscript{52, 161} and 2 primary care providers with addictions expertise (JM and TT).\textsuperscript{129, 179, 180} The CC Team will meet weekly and will be divided into two Teams for efficiency after the number of patients enrolled increases (6-12 months), based on experience with collaborative care for depression. Each CC Team will oversee 75 patients during the trial. Ongoing CC patients will be prioritized for discussion based on a risk-stratification algorithm that takes into account severity of alcohol use and medical co-morbidity as well as frequency of missed appointments. The CC Team will discuss: issues regarding medication use for alcohol dependence; medical, psychiatric or substance use co-morbidity; and decisions regarding when patients might need to be admitted (e.g. for withdrawal). The CC nurse and/or NP will document all CC Team consultations in a CPRS note, using electronic note templates that will be developed in the first nine months of the study to facilitate efficient documentation.

Role of the patient’s primary care (PC) provider. A potential benefit of using the CC delivery system for evidence-based care for AUD is to involve PC providers and increase their experience managing AUD. Primary care providers will be asked to indicate whether they wish to prescribe medications for alcohol dependence recommended by the CC Team. If so, the recommended orders will be placed in CPRS and the provider will be alerted to sign them. Our expectation is that, over time and with support from the CC Team, some providers will become comfortable writing or refilling medications for alcohol dependence. However, as noted above and found in depression collaborative care trials,\textsuperscript{181} many providers are expected to prefer to have the CC Team manage AUD.
Training. Dr. Ludman will lead training of the 2 CC nurse care managers (CC nurses) and the NP. CC nurses will be hired 16 hours a week (40% time) and trained specifically for this study. One NP will be recruited from the study clinics to devote 20% time to managing AUD. The training will be developed by Drs. Ludman, Kivlahan, Saxon, and Bradley and will represent a combination of training from previous CC trials, the COMBINE MM training, and the manual from a prior trial of lab monitoring. 52, 66, 71, 131, 136, 141, 142, 157-159, 171 Consistent with procedures found effective in trials of CC for depression, each CC nurse and NP will receive 40 hours of general instruction in all aspects of the intervention plus 40 hours of specific instruction (didactic and role play) in brief negotiation strategies. Each CC nurse will then implement the protocol with 2-4 pilot patients (depending on experience and demonstrated competence), and each will complete a minimum of 10 sessions under observation by Dr. Ludman prior to certification.

Usual Care. Patients randomized to Usual Care (UC) will have no study-related intervention and will only be contacted at 3 months and 12 months for telephone surveys about drinking and for labs at 12 months. They will have no other contact with study staff and will continue to get all VA care as usual. Usual Care patients may be referred by their regular providers for VA and non-VA alcohol treatment, as may CC patients.

Data Sources, Collection, Instruments, and Management.

Patient Assessments. In addition to the Brief Telephone Screen used for Step 2 of recruitment, all enrolled patients complete the following assessments at baseline: in-person visits including interviews, self-report surveys, and lab tests, followed by a telephone survey by an independent Survey Research Program. Follow-up telephone surveys will be completed 3 and 12 months after baseline, and labs will be obtained again only at 12 months follow-up. Table 12 summarizes assessments and indicates which data will be available to the CC nurses and NP; all data from telephone surveys conducted by an independent Survey Research Program will be used only for research purposes. Table 13 outlines all measures, sources and timing.

Brief Telephone Screen—Eligibility measures and race/ethnicity. Two validated screening questions about the frequency of drinking and heavy drinking, 182 adapted to ask about the past month, will be used to assess the frequency of heavy drinking: “During the last month, about how often did you drink any alcoholic beverages?” and “During the last month, about how often did you drink 5 or more drinks in a single day (4 for women)?” 183 Prior alcohol treatment will be assessed with a question from a prior VA primary care study, “Have you ever been in treatment or attended AA meetings for an alcohol problem?” 112, 184 Among patients who screen positive for unhealthy drinking, this question is associated with increased problems due to drinking at any given level of alcohol consumption. 112 Patients will also be asked their racial and/or ethnic background with the question used in the COMBINE study. 71 Patients will self-identify as Hispanic or non-Hispanic, and self-identify their racial group as White, African American or Black, Asian, Pacific Islander, Native American, or other. 171

Baseline Research Assessment. After written informed consent is obtained, the baseline in-person interview will assess select covariates and secondary outcome measures. Interviews will be conducted on paper for later double entry, and all interviews will be checked for completion before the patient leaves. Marital status, education, employment, and income will be collected using standard questions. 71 The brief, well-validated, 185-187 and widely-recommended Mini-Cog will be used to screen patients for dementia. 188, 189 Mini-Cog scores (0-5) have been associated with people’s ability to use the telephone 190 and patients with scores < 3 will be excluded from this study. The Mini International Neuropsychiatric Interview (MINI) will be used to assess: anxiety, depression, bipolar and psychotic diagnoses; substance-related disorders including alcohol; and post-traumatic stress disorder (PTSD). The MINI was designed as a brief but accurate structured psychiatric interview to identify the major Axis I psychiatric disorders outlined in the DSM-IV and International Classification of Disease 9th edition (ICD-9) diagnostic manuals. The MINI has a mean administration time of
16 minutes\textsuperscript{191} and good reliability and validity compared to longer assessments.\textsuperscript{192} \textbf{Prior help-seeking and treatment utilization for drinking} will be evaluated at baseline using the Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS) question with a lifetime time frame.\textsuperscript{6} \textbf{Family history of alcohol use disorders} will be assessed using a single question from the well-validated WHO Composite International Diagnostic Interview (CIDI) – Alcohol Use module.\textsuperscript{193} We will use the \textit{Health Utilities Index 3} (HUI-3),\textsuperscript{194} to measure eight domains of Health-Related Quality of Life (HRQoL). Although several other instruments for measuring HRQoL exist,\textsuperscript{195-197} we chose the HUI-3 because it is easy to administer and includes a cognitive dimension which may be sensitive to the intervention, and little evidence suggests one HRQoL measure is superior to another.\textsuperscript{198} We will measure HRQoL in-person at baseline and by telephone at 12 months. \textit{Patient travel to VA.} To estimate patient travel costs and time spent related to CC, patients will be asked where they travel from (e.g. home or work) for calculating the distance with Google®, and their mode of travel (bus, van, auto, taxi, other).

**Baseline self-administered surveys.** Self-administered surveys will be used to minimize participant burden and costs of collecting secondary measures, and will be completed at or before the in-person baseline interview. The Enrollment Coordinator will check all surveys for complete responses at the visit. Three mental health screens will be administered at baseline to permit comparison to other samples and to provide information for the CC nurses and NP. The \textit{10-item AUDIT} (0 to 40 points) assesses problem drinking severity and is widely used in research and practice.\textsuperscript{199-201} \textbf{The Patient Health Questionnaire 9-item Depression Screen (PHQ-9)} is a reliable and valid depression screen and reflects functional impairment from depression.\textsuperscript{202} The \textit{PTSD Checklist (PCL)} assesses symptoms of PTSD.\textsuperscript{203-210} \textbf{Prior alcohol treatment in specialty addictions settings} will be assessed with a question from the COMBINE Trial’s protocol for the initial MM visit.\textsuperscript{171}

Table 12. Modes of Data Collection and Instruments

<table>
<thead>
<tr>
<th>Data Collection Procedure</th>
<th>Instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Telephone Screen</td>
<td>*HDD screen (2 items), prior alcohol treatment or AA, race/ethnicity</td>
</tr>
<tr>
<td>In-person Baseline Assessment</td>
<td>Demographics, Mini-Cog, *MINI, treatment utilization (AUDADIS), family history, HUI-3, patient travel</td>
</tr>
<tr>
<td>Baseline Self-Administered Survey</td>
<td>*AUDIT, PHQ-9, PCL, Prior alcohol treatment (COMBINE)</td>
</tr>
<tr>
<td>Baseline &amp; 3 Month Telephone Surveys</td>
<td>Smoking, TLFB, SIP-R, 3-items re: readiness for, intention to and confidence in ability to change drinking</td>
</tr>
<tr>
<td>12 Month Telephone Surveys</td>
<td>Baseline &amp; 3 month telephone measures, AUDIT; two treatment utilization measures, HUI-3, AAAS, patient travel and time</td>
</tr>
<tr>
<td>Collected by care managers (CC only)</td>
<td>Personal support for change, preference for various aspects of care offered via CC (labs, medications, etc.)</td>
</tr>
</tbody>
</table>

*Bold instruments* indicate research assessments used by CC nurse care managers

**Telephone Surveys – Baseline, 3, and 12 months.** Telephone surveys will be used to collect main alcohol outcome variables at baseline, 3 months and 12 months, as well as secondary outcomes at 12 months. Telephone surveys will be conducted by the Group Health Cooperative Survey Research Program (SRP) to facilitate blinding. SRP is a state-of-the-art survey research group that offers computer-assisted telephone interviewing (CATI). The SRP’s CATI software Computer-Assisted Survey Execution System (CASES), is a
At baseline and 3 months, telephone surveys will be 5-20 minutes and include questions about health habits, alcohol consumption, problems due to drinking, and 3 items relating to readiness to change. At 12 months, additional measures will be added from other baseline assessments. **Health Habits.** Patients will be asked if they smoked cigarettes in the past year, and the average number of cigarettes per day, when they last had a drink containing alcohol, the frequency with which they exercised for 30 minutes or more, and whether they have followed a special diet, in the past 4 weeks. These are intended to build rapport before more sensitive alcohol-related questions. **The 28-day Timeline Follow-back (TLFB)** will be used to assess alcohol use in the past 4 weeks at baseline, 3 and 12 months. A 4-week timeframe is used so that all patients will be evaluating the same time period (i.e., the same numbers of weekdays and weekends) and to facilitate recall. The TLFB is a valid and reliable gold standard measure of consumption and has adequate reliability when administered via telephone.\(^{211, 212}\) In addition, the TLFB was used to assess main outcomes over the phone in a recent primary care trial in patients with AUD.\(^{57}\) Subjects will be asked to recall the type and number of standard drinks consumed on each of the previous 28 days. Patients will be provided a calendar at the baseline in-person visit as a prompt and sent a replacement for follow-up interviews. If a patient stopped drinking in the 28 days preceding the baseline assessment, drinking will be assessed for the 28 days prior to that day in order to obtain a reliable baseline estimate of drinking.\(^{71}\) Alcohol consequences will be measured using the **Short Inventory of Problems – Recent version (SIP-R),** which is a reliable, validated 15-item measure of drinking-related consequences derived from the longer Drinker Inventory of Consequences (DrInC).\(^{213, 214}\) Three single-item measures of **readiness to change, intention to change and confidence in ability to change** will be assessed at baseline, 3, and 12 months (all scaled 0-10).\(^{215-217}\) These brief measures correlate with longer measures and predict alcohol-related consequences in outpatients with unhealthy alcohol use.\(^{216, 218}\) Longer measures are not being used in order to minimize patient burden and potential assessment reactivity by eliciting self-motivational statements.\(^{219, 220}\)

At 12 months, the follow-up telephone survey will last 45 minutes on average and will also include the following baseline measures: AUDIT, two measures of treatment utilization, HUI-3, and travel time and employment and income. To assess the degree of engagement in 12-step programs, the 12 month telephone survey also includes a single item from the **AA Affiliation Scale (AAAS)** with the complete scale (9 items) for patients who attend 12-step programs.\(^{221}\)

**Instruments administered by CC Nurses (CC Patients only).** CC nurses will have standardized procedures for collecting additional data to inform their discussions with patients during CC and recommendations by the CC Team. Preference for medications, lab monitoring, and telephone visits will be adapted from the COMBINE **treatment preferences** questions assessed in the MM protocol.\(^{171}\) The COMBINE measure of **personal support for not drinking**\(^{171}\) will be modified for use in the initial CC visit.\(^{222, 223}\)

**Laboratory Testing.** Three laboratory tests reflecting heavy drinking will be collected at baseline and 12 months follow-up: **GGT, CDT, and MCV.**\(^{169}\) All labs will be drawn in the clinical labs at VA Puget Sound, but specimens for CDT testing will be sent to Medical University of South Carolina (MUSC). Laboratory tests will be used as a "bogus pipeline" to maximize the validity of self-reported consumption and will also be used as
secondary outcome measures. Additional lab tests of liver and renal function will be collected as part of CC for patients who elect to take medications for alcohol dependence.

**Secondary Data**

**VA Clinical and Administrative Data.** Secondary VA data will be obtained from 3 sources: 1) the local VA Computerized Patient Record System (CPRS); 2) VA’s National Patient Care Databases (NPCD); and 3) the Northwest (NW) data warehouse. **CPRS.** Alcohol screening data (individual responses and AUDIT-C scores), date of birth (DOB), gender, address, phone numbers, and scheduled future visits for addictions treatment will be obtained from the local electronic medical record on a weekly basis (CPRS). Over 90% of VA Puget Sound patients were screened for alcohol misuse with the AUDIT-C in 2008. **National VA Patient Care Databases (NPCD)** will be used to obtain all inpatient and outpatient ICD-9 diagnoses (for descriptive purposes), outpatient utilization, dates of all admissions and discharges (for utilization and cost analyses), all pharmacy and lab data (for analyses of the cost of the intervention), and data on vital status. Diagnoses and utilization data will be extracted from the medical SAS datasets inpatient treatment files (PTF) and outpatient care files (OPC) in the NPCD, whereas pharmacy data (medication and dose dispensed, date of dispensing, number of pills, duration, instructions, and prescriber), will be extracted from the Decision Support System (DSS). All VA cost data will also be obtained from the VA Vital Status Files, which combine data from the Beneficiary Identification Record Locator System (BIRLS) Death File, the Medicare Vital Status File (if available), the Social Security Administration Death Master File, and the VHA Medical SAS Inpatient Database. **Northwest (NW) data warehouse,** a local regional database of CPRS data, will be used to obtain all AUDIT-C data at follow-up (for secondary analyses on recruitment reactivity) and all data from CC nurse, NP, and CC Team progress note templates.

**Non-VA data sources.** Two non-VA sources of secondary data will be used. The **Washington State Comprehensive Hospital Abstract Reporting System (CHARS)** includes administrative hospitalization data for all 94 non-VA hospitals in Washington State. We will use CHARS to obtain data for non-VA inpatient utilization in the 12 months prior to randomization and during the 12-month study. CHARS includes date of admission, date of discharge, principal diagnosis and up to 8 more discharge diagnoses, and length of stay (LOS) in days and hours. Patients in the trial can be linked to CHARS using name, DOB, and last 4 digits of the social security number (SSN). The **Washington State Death File** will be used to supplement VA data on death for any patient lost to follow-up at the end of the study.

**Prevention of attrition.** Although patients with substance use disorders are notoriously challenging to follow over time, we will use a state-of-the-art intensive protocol to locate enrolled randomized subjects at 3 and 12 months. These procedures include obtaining detailed information at baseline regarding demographics for patients including all patient names, aliases, addresses and phone #s, as well as the names and phone numbers of relatives (≥2), friends/contacts (≥2), employers, and professionals with whom they interact. For each patient, we will obtain key identifiers (drivers license #), agency numbers (e.g. Medicaid), occupation, work address and phone, contact information (mail and phone), and permission to contact all of the above by phone, mail or in-person if necessary. Participants will receive information cards with study phone numbers and emails so they can notify the study if they move. Patients will be sent a $2 bill with a letter of introduction (baseline) or reminder letter (follow-up) a week before the interview to encourage them to schedule an interview, and they will receive incentives for participating as above. If necessary, research associates will leave the office to find participants at follow-up. Similar methods have resulted in 95% follow-up in a study of women with substance use disorders and in 89% follow-up at 1 year in a VA trial of referral to 12-step programs for patients with substance use disorders coordinated by a member of Dr. Bradley’s team.

**Data management.** Data tracking will be completed by research staff, and all study data will be managed by the study Data Manager, Dr. Sun. The Study Coordinator (Ms. Thomas) will develop and maintain a system for tracking potentially eligible patients. This tracking system will include: all inclusion and exclusion criteria, all recruitment steps and consents, results on the Brief Telephone Screen (if consent), patient interest in study, and scheduled appointment times with the Enrollment Coordinator. The Enrollment Coordinator will maintain a database for tracking all patients scheduled for in-person assessments. The Enrollment Coordinator will double enter all data from self-report questionnaires and in-person interviews and upload data daily to a secure server for further data management by Dr. Sun. The Enrollment Coordinator will provide lists, contact
information, and study IDs of all consented and enrolled patients to the Survey Research Program (SRP) for
telephone surveys. Finally, following consent and all required baseline assessments, including telephone
surveys by SRP and labs, the Enrollment Coordinator will contact the Project Director (Ms. Williams) for
randomization of patients into either Usual Care or Collaborative Care. Ms. Williams will open the
randomization envelopes and double enter patient group assignments into a randomization tracking database,
with randomization variables masked. Weekly she will provide an updated randomization list to Dr. Sun with
study ID linked to the masked randomization variable. Dr. Sun will maintain all master study databases, with
the exception of the randomization cross-walk data maintained by Ms. Williams. In addition to managing all
data collected by the study coordinator, the Enrollment Coordinator, and the Survey Research Team, Dr. Sun
will also obtain and manage all lab data and all clinical and administrative data from secondary data
sources. She will be primarily responsible for the integrity of all data, and will prepare reports for the 3-person
Data Safety Monitoring Board (DSMB) which will review all adverse events.

Measures

**Primary Outcome Measures.**

1. **Aim 1 Outcome – Number of Heavy Drinking Days (HDD) at 12 months.** The number of heavy
drinking days (HDD) reported in the 4 weeks prior to the 12 month interview will be the Primary Aim 1 outcome,
with HDD defined as 5 or more drinks in a day for men and 4 or more drinks for women. This measure,
derived from the 28-day TLFB, was chosen to be a sensitive, yet clinically meaningful measure of change
and to allow comparison to a previous study.

2. **Aim 2 Outcome – Abstinent or drinking below recommended limits without problems at 12
months (a “good drinking outcome”).** The outcome measure for Aim 2 will be a binary measure of a “good
drinking outcome” at 12 months, similar to a measure used in COMBINE but adapted to have a 28-day
timeframe. Drinking less than recommended limits will be defined based on NIAAA recommended limits
(< 14 drinks per week for men and < 7 drinks for women and no heavy drinking days). Problems due to
drinking will be measured based on the SIP-R. The original validation study of this measure allowed patients
2-3 slips when they drank above recommended limits or had alcohol-related problems over 3 months, so our
28-day version allows patients 1 slip, consistent with DSM-IV alcohol abuse requirements for recurrent
symptoms.

**Secondary Measures.**

a. **Measures of Engagement in Alcohol-Related Care. Use of medications for alcohol dependence.**
The numbers of both prescriptions and refills obtained for medications for alcohol dependence will be collected
for both the CC and Usual Care groups. Based on these numbers, two binary indicators of any medication
prescriptions and any medication use for alcohol dependence will indicate whether patients were prescribed
(irrespective of refills) and whether they obtained and refilled at least one prescription for naltrexone,
acamprosate or disulfiram during the study. To assess engagement in CC by primary care providers we will
also use a measure of the number of medication prescriptions ordered by primary care providers (initiated or
refilled). Lab monitoring. A continuous measure of the number of lab tests for lab markers will be used for
descriptive purposes. In addition, a binary measure for both the CC and Usual Care groups will indicate
whether patients had at least 4 blood draws at least 2 weeks apart for 1 or more of GGT, MCV, or CDT (with
CDTs available only to CC patients). VA addictions treatment. The number of visits for VA addictions
treatment and the number of inpatient days for VA alcohol treatment will be collected as a measure of formal
VA alcohol treatment in both CC and Usual Care groups. In addition, a binary indicator of engagement in
formal VA addictions treatment (inpatient or outpatient) in the 12 months after enrollment will be derived based
on VA NPCD data. For outpatient treatment, at least 2 visits in at least 3 consecutive months will be required
to consider patients to be engaged in specialty care. Other Alcohol-Related Help. A binary measure of
participation in 12-step programs will be derived from patient report of attending at least 3 meetings in the year
after randomization on the AAAS. A binary measure of seeking help for drinking in the previous 12 months
will be derived from patient report, based on the AUDADIS measure of treatment utilization assessed at 12
months. A composite binary measure of any alcohol treatment will be derived from the binary measures of
any medication use for alcohol dependence, engagement in VA addictions treatment, participation in 12 step
programs, or help-seeking for drinking during the 12 month study. Engagement with Collaborative Care
(CC). For patients randomized to CC, there will be three measures of engagement. A scaled measure of total number of CC visits based on CPRS notes will be used for descriptive purposes. We will also use a binary indicator of participation in at least 6 CC encounters (CC nurse and/or NP) over the first 3 months of treatment. Brown and colleagues found that about 50% of recruited patients with AUD engaged with repeated telephone BI to this degree.57 Finally, a binary measure of any engagement in CC will be derived based on binary measures above for CC visits, medications, or labs for CC patients. Any Engagement. For all patients, we will have a final binary measure of engagement in any alcohol-related care, which will be a composite of any alcohol treatment or any engagement in CC as defined above.

Table 13. Measures, Instruments, Data Sources, and Timing of Collection

<table>
<thead>
<tr>
<th>Measure</th>
<th>Instrument or Test</th>
<th>Data Source</th>
<th>Baseline</th>
<th>3 Month</th>
<th>12 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome Measures</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1. # Heavy drinking days (HDD)</td>
<td>28-day TLFB</td>
<td>Telephone survey</td>
<td>X</td>
<td>X</td>
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<tr>
<td>2. Good Drinking Outcome*</td>
<td>28-d TLFB, SIP-R</td>
<td>Telephone survey</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td><strong>Secondary Outcomes Measures</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>A. Process measures of engagement</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CC engagement (# visits)*</td>
<td>Treatment notes*</td>
<td>NW data warehouse</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Lab monitoring (# labs)</td>
<td>Laboratory</td>
<td>NPCD</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Medication use (# refills)</td>
<td>Pharmacy data</td>
<td>NPCD</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Any engagement CC (binary)*</td>
<td>Above 3*</td>
<td>NPCD</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>VA addictions Tx (# visits)</td>
<td>Utilization data</td>
<td>NPCD</td>
<td>X</td>
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<tr>
<td>12-step involvement (scaled)</td>
<td>AAAS</td>
<td>Telephone survey</td>
<td>X</td>
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<tr>
<td>Sought help for drinking (binary)</td>
<td>AUDADIS</td>
<td>Telephone survey</td>
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<tr>
<td>Any alcohol-related care</td>
<td>Any of above</td>
<td>NPCD &amp; phone int.</td>
<td>X</td>
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<tr>
<td>B. Secondary drinking measures</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Resolution of HDD*</td>
<td>TLFB</td>
<td>Telephone survey</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td>Drinking below weekly limits*</td>
<td>TLFB</td>
<td>Telephone survey</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Drinking below NIAAA limits*</td>
<td>Both 2 above</td>
<td>Telephone survey</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>% abstinence*</td>
<td>TLFB</td>
<td>Telephone survey</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>4 categories of problem drinking</td>
<td>28-d TLFB &amp; SIP</td>
<td>Telephone survey</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Motivation for change*</td>
<td>3 items</td>
<td>Telephone survey</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Alcohol screening at follow-up</td>
<td>AUDIT, AUDIT-C</td>
<td>NW data warehouse</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>C. Laboratory Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol-related lab values</td>
<td>GGT, MCV, CDT</td>
<td>CPRS; MUSC</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Abnormal lab results</td>
<td>GGT, MCV, CDT</td>
<td>CPRS; MUSC</td>
<td>X</td>
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<td></td>
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<tr>
<td>D. Health-related quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HUI-3</td>
<td>Interviews†</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>E. Health care utilization and costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Number of outpatient visits</td>
<td>Visits</td>
<td>NPCD</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Days hospitalized, VA &amp; non-VA</td>
<td>Admit, d/c dates</td>
<td>NPCD &amp; CHARS</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Cost of inpatient utilization</td>
<td>Admit, d/c dates</td>
<td>DSS &amp; CHARS</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. Cost of the Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost to deliver CC</td>
<td>Logs, notes, labs</td>
<td>CC RN logs†, NPCD</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost to the patient</td>
<td>Survey</td>
<td>Interviews†</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Abstinence or drinking < NIAAA recommended limits without problems; † 3 single-item questions about readiness, intention & confidence; ‡ In-person at baseline and telephone at 12 months; § CC patients only; † Last 4 weeks; ‡ Logs=timesheets.

b. Secondary Drinking Measures. Secondary drinking measures include outcomes at 3 months, secondary outcomes at 12 months, and variables to be used as covariates. Both primary outcome measures will also be measured at 3 months. The study is adequately powered to detect differential treatment effects at 12 months, but we evaluate primary outcome measures at 3 months to gain exploratory insight into changes in alcohol-related outcomes associated with CC. Three secondary binary measures, resolution of heavy drinking, drinking below recommended weekly limits and drinking below NIAAA limits (no HDD and < weekly limits) in the past 28 days, will be derived from the TLFB at both 3 and 12 months. The proportion of patients who are abstinent for the last 28 days will be measured at both 3 and 12 months, based on the previous lab monitoring study that resulted in high rates of abstinence despite the intervention not being abstinence-oriented.66
Patients will also be categorized based on a composite 4 category problem drinking scale: 1) abstenient; 2) non-risky drinking without problems; 3) heavy drinking or problems due to drinking; and 4) both heavy drinking and problems. Category 3 combines heavy drinking and problems because it is unclear how to prioritize patients with just one or the other. Slips will be allowed as above for the Primary Aim 2 outcome.\(^{234}\) We will use the full AUDIT as a secondary alcohol measure comparing CC and Usual Care groups, to test whether it might be useful to monitor outcomes in clinical practice. We will use the first AUDIT-C score at follow-up screening (10-24 months after baseline) as a scaled measure of drinking at follow-up (scores range 0-12), to evaluate whether efforts to recruit patients to this study (letter, Brief Telephone Screen, etc.) are associated with changes in reported drinking. We will use three scaled measures (0-10) to assess each patient’s report of readiness to change, intention to change and confidence in his or her ability to change at 3 and 12 months.\(^{215,216,218}\) These measures will be used because some patients who have not changed may have increased readiness to change.

**c. Measures of Changes in Laboratory Markers of Heavy Drinking.** Measures of changes in laboratory markers of heavy drinking will be used as secondary outcomes. Results of GGT, MCV and CDT laboratory tests at 12 months will be used as a secondary outcome in all patients. In addition, binary measures of resolution of abnormal alcohol-related labs will be derived for each type of laboratory test (GGT, CDT or MCV) individually, and a single binary measure will be derived to represent resolution of all abnormal labs, for patients with abnormal lab markers at baseline.

**d. Measures of Health Related Quality of Life.** Eight domains of health-related quality of life (HRQoL) will be derived from the HUI-3. If CC decreases problems due to drinking, it could improve HRQoL.\(^{160,236,237}\) However, because the effect of reduced drinking is likely reflected in longer patient survival even if HRQoL measures do not change during the trial, we will use a continuous measure of quality-adjusted life years (QALYs) to estimate adjusted differences in the 2 groups (CC and Usual Care) at 12 months, an approach which allows comparisons of HRQoL that take survival into account. QALYs for each group will be calculated by connecting the quality-of-life scores for each patient (baseline and 12 months) with straight lines and calculating the area of the resulting trapezoid. For patients who die (estimated 1.5%) during the year of follow-up, HRQoL scores will be assigned a value of zero at the time of death.

**e. Measures of Health Care Utilization and Direct Inpatient Medical Costs.** Continuous measures of the numbers of outpatient visits to VA primary care, mental health clinics, and addictions treatment will be evaluated for descriptive analyses and to compare CC and Usual Care groups. Because the intervention could be associated with decreased hospitalizations or decreased lengths of inpatient stays,\(^{236,239}\) days hospitalized in the year after randomization will be used as an overall measure of health care utilization for both CC and Usual Care groups. This measure will be based on administrative data from all VAs (NPCD) and all hospitals in Washington State for the year before (baseline measure) and the year following randomization. The number of hospitalizations for an alcohol-related diagnosis will be based on ICD codes from discharge diagnoses and will also serve as a secondary measure. For this study, as in a previous study by co-investigators,\(^{195}\) total VA inpatient, outpatient, laboratory and pharmacy costs will be assessed from DSS. We will calculate costs of VA and non-VA inpatient health care utilization using length of stay, and DSS data for costs of VA hospitalizations and Medicare cost-to-charge ratios for each hospital for non-VA hospitalizations. DSS calculates costs for each medical center based on actual expenditures.

### 2. Measures of the Cost of the Intervention

If the CC intervention is effective, health care systems will be interested in its estimated cost and results of cost effectiveness analyses (CEA). While CEA are beyond the scope of this initial trial, we will estimate costs to deliver the CC intervention and costs of the intervention to patients.

We will measure costs to deliver the CC intervention, including all direct medical costs, using a combination of micro-costing strategies used in previous alcohol and CC trials.\(^{73,107,162,238,239}\) Costs of personnel will include salary, benefits and overhead (e.g., office space) for all study personnel, pro-rated for the time they spend on screening, assessment, CC visits and CC team meetings (using VA salaries for clinicians supported by VA for this study). Time for CC nurses and NPs will be collected using time sheets which capture time for direct patient care and other CC-related activities.\(^{161}\) Training and supervision time will be recorded on training logs. To estimate costs of medications we will use the average wholesale price for medications based on Medicaid pricing rules,\(^{240}\) and lab costs will be based on the Medicare Fee Schedule. Time spent on issues...
related specifically to the trial (e.g., assessments not used by the CC nurse, IRB issues and analysis of data) will not be included.\textsuperscript{73, 162}

We will also measure patient costs using patient time spent on the intervention visits (phone or in-person), and direct non-medical costs of travel to and from the VA for CC or lab tests. Visit notes and labs (and dates) will be identified in CPRS, and travel time will be assessed from patient surveys at baseline and 12 months. We will use age and gender-specific average wage rates to value patients’ time. Travel costs will be based on patient reports on mode of transportation to the VA, costs of each mode (AAA for auto, bus fare, etc.) and the geo-coded distance between patient’s ZIP code and the VA.

Measures used for Descriptive Analyses and as Covariates

Measures of demographic characteristics will include age, gender, race (NIH categories), marital status, employment status, and income. A measure of current smoking status will be derived from smoking questions on baseline telephone surveys. Patients will be classified as current smokers if they smoked in the past year. A continuous measure of packs per day on average (PPD) will be derived for patients classified as current smokers. Patients who report problems with alcohol use in their biological parents, brothers or sisters, or children will be considered to have a family history of alcohol use disorders. Psychiatric Co-morbidity will be based on the MINI. Patients will be classified based on the following DSM-IV psychiatric diagnoses in the past year: major depression, general anxiety disorders, panic disorders, PTSD, AUD, and non-alcohol, non-tobacco substance use disorders. Measures of clinically diagnosed medical and psychiatric co-morbidity will be based on ICD codes from the past year in VA administrative databases and will be used to describe the study population. We will determine death during 12 months follow-up from VA and Washington State death records.

Statistical Analyses

All data collected will be screened for outliers and nonsensical values. Descriptive statistics and graphic procedures will be used to inspect distributions to ensure that they meet assumptions of statistical tests and estimation procedures. Baseline measures will be compared between CC and Usual Care groups.

Missing Data. We will make every effort to obtain complete data on each study participant at both follow-ups, as described above. However, some missing data at follow-up is inevitable and creates a risk for selection bias that can skew results. Our initial primary and secondary analyses will only include patients with complete data. We will also analyze baseline patient and clinical factors that are associated with having a missing value and perform sensitivity analyses by 1) imputing missing values using multiple imputation (MI) based on Markov Chain Monte Carlo (MCMC) methods,\textsuperscript{241} 2) assuming that any patients lost to 12-month follow-up continued to drink at their baseline levels and 3) assuming any patients lost to 12-month follow-up continued to drink at their most recently assessed level from either baseline or 3-month follow-up. We will compare these results to the complete-case results to determine if inference differs substantially. Use of MI methods will provide valid results when the likelihood of missingness is dependent on observed variables but not on the unobserved variables.\textsuperscript{241, 242}

Analyses of Primary Outcomes

Aim 1. Compare the Number of Heavy Drinking Days (HDD) in the past 28 days.

Primary intent-to-treat analyses for Aim 1 will compare the mean number of heavy drinking days (HDD) in the past 4 weeks between the Collaborative Care (CC) and Usual Care (UC) groups at 12 months. For this comparison, we will fit a generalized estimating equation (GEE) adjusted for age at baseline, HDD at baseline, and randomization stratification variables (gender, binary indicator of abnormal laboratory biomarkers at baseline, and whether the patient met criteria for DSM-IV alcohol dependence at baseline). Although clustering at the primary care provider-level is not expected to be clinically or statistically meaningful, we selected the GEE model in order to adjust the variance estimate for the possibility that outcomes of patients who are seen by the same providers will be correlated.\textsuperscript{243} The mean model for the GEE is:

\[ E(Y_{ij}) = \beta_0 + \beta_1 X_{ij1} + \beta_2 X_{ij2} + \beta_3 X_{ij3} + \beta_4 X_{ij4} + \beta_5 X_{ij5} + \beta_6 X_{ij6} \]

where

\[ E(Y_{ij}) \] is the expected value of the response;

\( Y_{ij} \) = number of HDD at 12 months;

\( X_{ij1} \) = gender;

\( X_{ij4} \) = binary indicator of abnormal lab at baseline;
$X_{ij1}$ = group assignment (CC vs UC); $X_{ij5} =$ DSM-IV alcohol dependence at baseline;

$X_{ij2} =$ baseline HDD; $X_{ij6} =$ age at baseline.

A Gaussian variance will be used for the mean response, and we will initially assume an independent working correlation model. We will check inferences for the parameters by comparing parameter robust standard errors with respect to different covariance assumptions to determine whether they differ substantially. Our main goal is to test whether $\beta_i = 0$, where $\beta_i$ is the difference in mean HDD at 12 months between the CC and Usual Care groups.

**Aim 2. Analyses of the proportion of patients with a “Good Drinking Outcome”**. Primary intent-to-treat analyses for Aim 2 will compare the proportion of patients who are abstaining or drinking below recommended limits without problems (“good drinking outcomes”) at 12 months. Similar to Aim 1 analyses, we will fit a GEE model for binary outcomes in order to account for potential correlation of outcomes at the level of primary care providers. 243 This model will be adjusted for the same covariates as above, with the exception that to adjust for baseline values of the Aim 2 outcome we will omit HDD and instead include the 4 category measure of problem drinking based on the components of the Aim 2 outcome measure. The mean model for the GEE is the following:

$$\logit(E(Y_{ij})) = \beta_0 + \beta_1 X_{ij1} + \beta_2 X_{ij2} + \beta_3 X_{ij3} + \beta_4 X_{ij4} + \beta_5 X_{ij5} + \beta_6 X_{ij6}$$

where $\logit$ is the link function for binary data and $E(Y_{ij})$ is the expected value of the response; $X_{ij3}$ - $X_{ij6}$ are as above for Aim 1.

$Y_{ij} =$ indicator of a good drinking outcome at 12 months; $X_{ij1} =$ group assignment (CC vs UC);

$X_{ij2} =$ the 4 category measure of problem drinking from which the binary outcome is derived.

We will use a binomial variance for the mean response and will initially assume an independent working correlation model, but will check inferences as above. Our main goal is to test whether $\exp(\beta_i) = 1$ where $\exp(\beta_i)$ is the population average odds of having a good drinking outcome at 12 months in the CC as compared to the Usual Care group.

**Secondary Analyses**

**1. Secondary Outcomes Compared via Intention to Treat Analyses**

**a. Process measures of engagement in alcohol-related care.** We will compare CC and Usual Care groups with regards to medication use for alcohol dependence, lab monitoring, participation in 12 step programs, any VA alcohol treatment (inpatient or outpatient), and any of these alcohol treatments available to CC and Usual Care using similar regression methods as outlined for main Aims 1-2 above. For each outcome, the baseline measure of the outcome will be used as a covariate. We will also compare CC and Usual Care groups with regards to receipt of any alcohol treatment (as defined above) during the 1 year study. We will also conduct descriptive analyses of each element of care for AUD received by each group.

**b. Secondary drinking outcomes.** We will compare CC and Usual Care groups with regards to 5 drinking outcomes and 3 measures of patient-reported readiness to change, intention to change, and confidence in ability to change. Analyses of binary measures will use the approach used for Aim 2, whereas the approach used for Aim 1 will be used for continuous or scaled outcomes. In each analysis, baseline values of the outcome will be included in models instead of baseline values of the Main Aim 1-2 outcomes.

**c. Laboratory outcomes.** We will fit GEE models as in Aim 1 to evaluate alcohol-related laboratory values at follow-up, adjusted for the baseline lab values as covariates (instead of HDD at baseline). Among patients with abnormal baseline laboratory values, we will fit a GEE model for binary outcomes to compare CC and Usual Care groups regarding resolution of abnormal labs.

**d. Health-related Quality of Life.** We will compare HRQoL and QALYs at 12 months follow-up in CC and Usual Care using similar methods as for Aim 1, adjusting for HUI-3 score at baseline (instead of HDD at baseline). 244

**e. Health care utilization and costs.** Numbers of outpatient visits, days hospitalized, and costs of inpatient health care utilization will be modeled using appropriate methods based on the distribution of the
data. To account for the skewed nature of utilization and cost data, we will follow the algorithm suggested by Manning et al.,\textsuperscript{245, 246} to choose between least-squares models on log transformed utilization and cost measures or generalized linear models with appropriate link and family assumptions. However, if there are many observations with zero visits, days hospitalized or costs for a category, then we will use two-part models in which the effect of the intervention on the probability of incurring any visits, hospitalization, or costs is estimated first, and the effect of the intervention on the number of visits, days hospitalized or costs for those who had outpatient visits, inpatient stays, or incurred costs is estimated second.

2. Cost of the intervention.

Ultimately, a proper cost-effectiveness analysis (CEA) of the proposed intervention would be essential.\textsuperscript{101} However, given the need to first demonstrate the effectiveness of the intervention for decreasing drinking, the proposed study will take just the initial step of estimating the cost to deliver the intervention and the cost of the intervention from the perspective of the patient, in addition to the analyses of the association of the intervention with VA and non-VA health care costs and QALYs above. As recommended, our descriptive cost analyses will include evaluation of intervention costs, direct medical costs, direct non-medical costs (e.g. patient travel costs), and patient time costs.\textsuperscript{247}

Other Secondary Analyses

Analyses of recruitment reactivity. Despite efforts to minimize alcohol assessments in this study, reactivity due to alcohol assessments and ethically required BI in the Brief Telephone Screen for recruitment could cause a decrease in reported drinking by the Usual Care group at follow-up. We have designed the study such that there will be large numbers of men potentially eligible who are not selected for screening (“no contact group”). To estimate potential reactivity from all recruitment efforts, we will compare follow-up AUDIT-C scores from secondary VA data sources between men who were randomly omitted from recruitment and those eligible to be screened by telephone. Only men screened with the AUDIT-C in a VA clinical setting during the first year of recruitment will be eligible for these analyses in order to allow ample time for follow-up visits with repeat annual clinical alcohol screening with the AUDIT-C (up to 2.5 years). Similar to Aim 1, we will fit GEE models adjusted for baseline AUDIT-C score and time between AUDIT-C screens.

As-treated analyses. Because of the encouragement trial design of this study, whereby we are simply offering a treatment, we will conduct secondary analyses to evaluate whether engagement with the intervention is associated with improved outcomes.\textsuperscript{226} Standard “as-treated” analyses that compared outcomes between patients who actually receive treatment and those who do not—regardless of randomization—would be inherently biased due to self-selection. To assess the association between engagement in alcohol-related care and the main study outcomes, we will employ Rubin’s Causal Model, a statistical framework for causal inference that addresses the limitations that result from self-selection bias in some “as-treated” analytic methods.\textsuperscript{248-250} The approach is a special case of the principal stratification framework\textsuperscript{251} and reduces to the instrumental variables analysis or a structural equations analysis under specific conditions.\textsuperscript{252} We will undertake 3 independent analyses to evaluate the association between engagement in alcohol-related care and primary outcomes using 3 binary measures of engagement: (1) any engagement in alcohol-related care; (2) any engagement in medication use for alcohol dependence; and (3) any engagement in CC care (visits, lab monitoring or medications). These analyses will be adjusted for baseline covariates and will utilize Bayesian and multiple imputation methods for inference that have been developed for this setting.\textsuperscript{253, 254} As above, models will adjust variance estimates to address correlated data.

Analyses of potential moderators of main outcomes. For each of the primary analyses, we will evaluate whether 4 hypothesized binary “moderators” interact with the intervention (“effect modification”) by including a treatment by moderator interaction term in separate GEE regression models for each of the following 4 potential moderators: (1) gender; (2) lab abnormalities at baseline; (3) DSM-IV alcohol dependence at baseline; and (4) prior alcohol treatment at baseline.

Power and Sample Size

Aim 1. We calculated the sample size for the proposed study in order to be well-powered to evaluate the primary outcome (Aim 1), which is the number of heavy drinking days (HDD) in the 28 days preceding the 12 month interview. We hypothesize that patients offered CC will have fewer HDD compared to patients who received Usual Care. We consider the minimum clinically meaningful difference to be a decrease of 4 HDD over a 4 week period (an average difference of 1 HDD per week) with a maximum standard deviation of 8.2-
8.5. Our calculations account for potential correlation of HDD among patients with the same primary care provider by assuming a conservative intra-class correlation coefficient of 0.05 and 8 patients per primary care provider. This is conservative since previous CC trials have observed no meaningful correlation. We conservatively estimate attrition to be <15%, which is greater than other trials of CC for depression with assessments done by the SRP trials of CC for depression in VA, and studies of primary care patients with AUD. To have 90% power (with a two-tailed alpha of 0.05), we require 150 patients per group for a total of 300 patients. Table 11 (above) shows that we estimate that 125 women and 971 men will be eligible and interested in enrolling in this study at the end of the Brief Telephone Screen (33%), which is a conservative estimate compared to a previous study of primary care patients with AUD. Previous AUD and CC trials have recruited more than 80% of patients at the final step of enrollment after stepped screening and consent. If we similarly recruit over 80% of eligible patients at the final step, we would enroll 100 women and 200 men. These analyses show that we have more than an adequate sample of eligible patients to achieve 90% power for Aim 1 analyses.

Aim 2. The natural history of drinking in the study sample is unknown, including what proportion of recruited primary care patients who receive Usual Care will be abstaining or drinking below recommended limits without problems (“good drinking outcomes” or GDO) 1 year after enrollment. We therefore calculated the detectable benefits for our composite binary measure of GDO across a range of prevalence rates for GDOs in the Usual Care group (Table 14), assuming > 80% power (2-tailed alpha 0.05). The highest possible response in the Usual Care group is assumed to be 60%, and the lowest 10%, although previous research suggests intermediate rates. If the proportion of Usual Care patients with GDOs is only 10% we will have 80% power to detect an absolute increase of 16%. If the proportion of Usual Care patients with GDOs is as high as in the COMBINE trial (60%), which recruited patients ready for abstinence-oriented medication treatment—an unlikely outcome in this population-based trial—the detectable absolute increase would be 19%.

<table>
<thead>
<tr>
<th>Table 14. Detectable Absolute Increases in GDO with Varying Assumptions about Change in the Usual Care Group (assuming 80% power)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion Good Drinking Outcomes (GDOs) in Usual Care Group</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Proportion CC with GDO</td>
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<tr>
<td>Absolute increase GDO</td>
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</table>

Study Limitations and Strengths

Efficacy/Effectiveness Trade-off. Whereas there would be many benefits to conducting an efficacy trial whereby we would test a highly specified and regulated intervention in a narrowly defined population, the proposed study is an “effectiveness trial” which seeks to test a care-delivery system in a real world clinical setting. Therefore, the study does not include a homogeneous population, a run-in period to identify adherent patients, extensive training and monitoring to ensure consistency and integrity of the intervention, and frequent research assessments and contacts to enhance participation. Instead, the proposed effectiveness trial will identify patients with a brief practical screen with few exclusions. In addition, CC nurses and NPs will be trained in practical protocols based on Collaborative Care for depression and COMBINE’s medical management intervention, and training will not include advanced counseling skills that would impede replication outside research settings. While this will not clarify the “active ingredients” of the intervention, we believe the effectiveness trial design is the appropriate design for this study because we are not seeking to determine what works, but instead are seeking to determine how to make evidence-based care widely available.

Unknown Rates of Engagement. While 66% of VA patients with heavy drinking report wanting help with their drinking, the only way to know whether patients will actually engage with a specific type of alcohol-related care is to offer it. Because we have not yet offered Collaborative Care for patients with AUD, we have not been able to test the proportion of patients who will engage. We know that addressing patients’ own agendas increases engagement in alcohol treatment, and that patients come to primary care seeking medical care. As a result, we have developed an intervention that takes an explicit medical focus, which we believe will result in high rates of engagement. Interventions with similar medical foci have been associated with high rates of engagement and improved drinking outcomes. Moreover, the proposed trial will not
only test whether CC improves drinking outcomes but will also measure proportions of patients who engage, thereby addressing important unanswered questions related to processes of and levels of engagement with care. As a consequence, even in the unexpected situation of a negative trial, findings will be rich.

**Risks of “Contamination.”** The unit of randomization in this study is patients to maximize statistical power. Patient-level randomization risks contamination due to providers’ seeing the benefits of the collaborative care intervention offered to some of their patients, and thereby potentially changing the care they offer to Usual Care patients. We decided to randomize patients instead of providers or clinics based on Dr. Ludman’s research showing that primary care providers have minimal impact on depression outcomes. In addition, contamination is expected to be minimal in the proposed study because each of the evidence-based practices requires planned frequent visits, active engagement of patients around their drinking, and use of medications that providers are uncomfortable prescribing. In order to address the possibility of contamination, however, we will measure all treatment received based on 12 month follow-up surveys and administrative data and therefore be able to detect changes in care over time in the Usual Care group that might be attributable to contamination.

**Generalizability.** Some may question whether studies that test systems of care-delivery within large integrated health care systems produce generalizable results. Just as the National Institute of Mental Health has answered that question with a resounding “yes” for depression, we believe the same is true for development of new systems of care for AUD. Although this first trial includes an interdisciplinary CC Team, which will not be available in many settings, the role of the interdisciplinary team will decrease over time as algorithms for care provision are developed. In addition, the powerful core of the intervention will be a nurse care manager and NP prescriber. Most small primary care practices have nurses, and many have NPs or physician assistants, who actively manage chronic diseases. More and more small practices have electronic medical records and systems for population-based preventive care. The intervention tested in this trial could be implemented by such teams with consultation from local mental health providers.

Further, although we believe that the VA is the optimal setting for this study, conducting the study at the VA represents both a strength and limitation. Because of the characteristics specific to both the veteran population and the nationwide system of care, generalizability of our results may be limited by use of the VA setting. However, partly as a result of our research, the VA has a strong foundation of alcohol screening and BI on which to base this next step: offering evidence-based treatments to patients at high risk for AUD who do not respond to BI. While Dr. Ludman has over 10 years experience conducting trials of CC for other mental health disorders at the Group Health Cooperative, and Dr. Merrill has implemented care for other substance use disorders in primary care at Harborview Medical Center (HMC), neither of those health care systems has yet implemented screening and BI on which to build collaborative care for AUD. Further, VA providers are eager for the intervention, and clinical leaders have agreed to allow research time to support essential VA co-investigators. Finally, our experienced team of VA and NIH investigators will take lessons from this study to a follow-up study in GHC or HMC.
II. Changes to Protocol
Changes Made During Preparation Prior to Study Initiation

The following changes were made based on VA regulations or discussions with consultants prior to study initiation.

Eligibility and Recruitment

1. Added exclusion criteria: VA employees (per VA requirements), suicide risk flag in medical record, and no primary care provider.
2. Changed age inclusion criteria to ≤75, and AUDIT-C score inclusion criteria to ≥4 for women (remained ≥5 for men).
3. Clarified pregnancy exclusion criteria applied only to women at the time of enrollment (women who became pregnant during the study were eligible to continue to participate).
4. Patients whose providers who did not respond to the request for permission to enroll their patients within 4 weeks became eligible for recruitment (without provider permission).
5. Patients’ primary care providers were given the option of signing the recruitment letter to their patients.
6. Health care providers were given the option to refer patients to the study.
7. Patients were not able to opt out of study participation via email, per VA Privacy Office.
8. The Brief Telephone Screen did not include Brief Intervention [BI], as the study staff performing screening were not qualified clinical staff.
9. Patients were not asked racial or ethnic background questions at the time of screening.
10. Patients were not given the option of completing the self-administered portion of the baseline survey prior to the in-person baseline appointment (to protect privacy by not mailing materials).
11. Baseline data were collected by an enrollment coordinator, no telephone interviews were administered at baseline.
12. The incentive for completing the baseline appointment was increased from $10 to $20.

Randomization

1. Randomization was not stratified by any abnormal biomarker at baseline (GGT, CDT or MCV), but was stratified additionally by primary care clinic location.
2. Randomization envelopes were not used; treatment assignment was concealed via computer and assigned by a study coordinator (not involved in baseline interviews) after all baseline procedures were completed.

Data Collection

1. Health Related Quality of Life was assessed by SF-12 instead of the HUI-3.
2. Mental Health Comorbidity measures were added to baseline (MINI, PHQ-9, PCL) and some repeated at 12 months.
3. A Social Network Support assessment was added at baseline (the Important People Inventory).
4. Demographic questions were added at baseline (some repeated at 12 months): marital status, education, race/ethnicity, income and employment.
Changes Made Following Study Initiation

Eligibility and Recruitment

1. Patients were allowed to self-refer to the study to be inclusive of patients who wished to join. Self-referred patients were then screened for eligibility the same was as patients proactively recruited.

2. VA Puget Sound has multiple primary care clinics. We began at just two sites, but created our database to allow adding more if necessary. Mount Vernon clinic was added as an additional recruitment study site in June 2012.

3. We reduced the required number of collateral contacts from 4 to 2 to increase recruitment and generalizability (many patients were isolated without 4 collaterals).

Analyses

1. Addressing Missing Data. The primary analysis approach was changed from a complete case analysis to multiple imputation. The rationale for this change was recent literature on the implications of missing data for alcohol research that recommended multiple imputation and maximum likelihood approaches for handling missing data. {Hallgren, 2013 #20262} {Witkiewitz, 2014 #20263} This recommendation is in accordance with the broader statistical literature highlighting the limitations of complete case analyses and single-imputation approaches such as the last observation carried forward (LOCF). {Little, 2014 #19809}, This change was made prior to conducting any analyses of outcome data.
III. Statistical Analysis
CHOICE Trial – Statistical Analysis Plan

Clinical trial registry/ID: ClinicalTrials.gov NCT01400581

Overview:

Scientific background and explanation of rationale: Alcohol use disorders are common and often chronic and relapsing conditions associated with substantial morbidity, mortality, and cost. Although specialty treatment improves outcomes and decreases health care costs for patients with alcohol use disorders, most patients with alcohol use disorders never receive treatment. Two types of evidence-based care for alcohol use disorders could be offered in primary care and are outlined in the 2007 NIAAA Clinicians Guide: (1) repeated brief interventions and (2) FDA-approved medications for alcohol dependence, combined with medical management. How these practices should be integrated into primary care settings is unknown. One possible approach is collaborative care, an intervention that has been proven to be effective for delivery of evidence-based primary care for depression. However, to our knowledge, collaborative care has not been tested for management of alcohol use disorders in primary care. We hypothesized that collaborative care could increase engagement of primary care patients with alcohol use disorders in evidence-based alcohol-related care, and thereby improve drinking outcomes. To test this hypothesis, we conducted a randomized controlled trial of a collaborative care intervention for alcohol use disorders in 300 adult patients who are actively engaged in primary care in the VA.

Specific objectives or hypotheses: We will test whether patients offered collaborative care relative to usual care:

1. Have fewer heavy drinking days at 12 months follow-up; and
2. Are more likely to be abstinent or drinking below recommended limits without problems at 12 months follow-up.

As secondary outcomes we will evaluate whether patients offered collaborative care relative to usual care have:

(a) increased engagement in care for alcohol use disorders at 12 months follow up
(b) improvements in pre-specified secondary drinking outcomes
(c) improvements in laboratory markers at 12 months follow up
(d) improvements in health-related quality of life at 12 months follow up
(e) decreased health care utilization over 12 months follow-up

Trial design and allocation ratio: Individually-randomized, parallel group design of collaborative care versus usual care, assigned in a 1:1 ratio.

Important changes to methods after trial commencement (such as eligibility criteria), with reasons: A new site was added to meet recruitment goals.

Participants:

Eligibility criteria:

Inclusion criteria:

1. AUDIT-C score ≥5 for men; ≥4 for women
2. Age ≤75 years at the time of AUDIT-C screening
3. Frequent Heavy Drinking based on patient report at Brief Telephone Screen, including at least:

- 8 heavy drinking days in the past four weeks (>5 drinks in a day for men; >4 women) OR
- 4 heavy drinking days in the past four weeks and documentation of prior alcohol treatment or attendance at AA

Exclusion criteria:

1. Missing address or phone in VA’s Computerized Patient Record System (CPRS)
2. Warning flag regarding violent behavior in CPRS
3. Patient participating in addictions treatment (VA or non-VA)
4. Primary care provider or patient indicates not to contact patient
5. Barriers to telephone assessment: hearing problem; non-English speaking
6. Unable to provide adequate collateral contacts (defined as 2)
7. Cognitive impairment based on MINICOG < 3
8. Unstable or acute medical, surgical or psychiatric problem requiring emergent treatment; including patients who have a suicide risk flag in their medical record (required by IRB/patient safety)
9. Not available for follow-up: planning to move within year; life expectancy < 1 year; enrolled in hospice
10. Pregnancy
11. VA employee

Changes in eligibility criteria from funded grant proposal:

<table>
<thead>
<tr>
<th>Change</th>
<th>Time frame when changed</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed inclusion criteria from age &lt;65 to age ≤75 years</td>
<td>5/19/2011: Before start of trial</td>
<td>Recommendation of consultant (Dave Oslin)</td>
</tr>
<tr>
<td>Changed AUDIT-C cutoff for women from ≥5 to ≥4</td>
<td>5/19/2011: Before start of trial</td>
<td>To increase numbers eligible and due to epidemiological literature suggesting marked under-reporting of drinking</td>
</tr>
<tr>
<td>Added new site (Mt. Vernon)</td>
<td>5/29/2012: After start of trial</td>
<td>To meet recruitment goals</td>
</tr>
</tbody>
</table>

Settings and locations where the data were collected: Patients were recruited from VA Puget Sound Primary Care Clinics. VA Puget Sound is a multi-site facility that in fiscal year 2008 cared for 34,703 primary care patients in 5 clinics at 3 locations, Seattle, Tacoma, and Mount Vernon, Washington
**Interventions:**

**Usual Care.** Patients randomized to Usual Care (UC) will have no study-related intervention and will only be contacted at 3 months and 12 months for telephone surveys about drinking and for labs at 12 months. They will have no other contact with study staff and will continue to get all VA care as usual. Usual Care patients may be referred by their regular providers for VA and non-VA alcohol treatment, as may CC patients.

**Collaborative Care (CC) Intervention.** The Collaborative Care (CC) intervention is a team-based delivery system for evidence-based primary care for AUD (details in Grant)

**Outcomes:**

*Pre-specified primary and secondary outcomes:*

<table>
<thead>
<tr>
<th>Outcome name</th>
<th>Data variable name</th>
<th>Type</th>
<th>Data source</th>
<th>Additional details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of heavy drinking days (HDD) in the past 28 days at 12 months follow-up</td>
<td></td>
<td></td>
<td></td>
<td>We plan to use a normal approximation because (1) it is more common in the literature, and (2) it is easier to interpret the resulting risk difference as compared to an odds ratio. However we will inspect the distribution and if there are large departures from normality we will treat this as a binomial outcome (number of HDD out of number of days at risk of heavy drinking)</td>
</tr>
<tr>
<td>Good drinking outcome (GDO) at 12 months follow-up</td>
<td></td>
<td>Binary</td>
<td>Derived from 28-day TLFB, SIP-R; Defined as abstinence or drinking below NIAAA recommended limits without problems in past 28 days</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>(Restricted to those possible in both groups)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(A) Process measures of engagement at 12 months follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any medication use</td>
<td>Binary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmacy data (NPCD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whether they obtained and filled at least one prescription for naltrexone, acamprosate or disulfiram during the study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any medication refill</td>
<td>Binary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmacy data (NPCD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Whether they obtained and refilled at least one prescription for naltrexone, acamprosate or disulfiram during the study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lab monitoring</td>
<td>Binary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laboratory data (NPCD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indicator of whether patients had at least 4 blood draws at least 2 weeks apart for 1 or more of GGT, MCV, or CDT (with CDTs available only to CC patients) not research labs at baseline and follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engagement in formal VA addictions treatment (inpatient or outpatient)</td>
<td>Binary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Utilization data (NPCD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 or more visits in VA addiction treatment center or inpatient admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participation in 12-step programs</td>
<td>Binary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Telephone survey</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Derived from patient report of attending at least 3 meetings in the year after randomization on the AAAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sought help for drinking</td>
<td>Binary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Telephone survey</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Derived from patient report, based on the AUDADIS measure of treatment utilization assessed at 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any alcohol-related care aside from CHOICE care</td>
<td>Binary</td>
<td>Any of the above, except for “lab monitoring” and “sought help for drinking.” Lab monitoring was excluded (decision: 2/19/16) but to be kept as an individual outcome for descriptive purposes. “Sought help for drinking” was excluded, because patients may refer to specific CHOICE care in their self-report (e.g., talking with a researcher from CHOICE)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>(B) Secondary drinking outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcomes at 3 months follow up</td>
<td>See above</td>
<td>Telephone survey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HDD in past 28 days at 12 months follow up</td>
<td>Binary</td>
<td>Telephone survey</td>
<td>Derived from 28 day TLFB; As in primary outcomes, we will exclude days with inpatient hospitalizations from the denominator</td>
<td></td>
</tr>
<tr>
<td>Percentage of days abstinent in past 28 days at 12 months follow up</td>
<td>Continuous</td>
<td>Telephone survey</td>
<td>Derived from 28 day TLFB; As in primary outcomes, we will exclude days with inpatient hospitalizations from the denominator</td>
<td></td>
</tr>
<tr>
<td>Resolution of HDD in past 28 days at 12 months follow up</td>
<td>Binary</td>
<td>Telephone survey</td>
<td>Derived from 28-day TLFB</td>
<td></td>
</tr>
<tr>
<td>Drinking below weekly limits in past 28 days at 12 months follow up</td>
<td>Binary</td>
<td>Telephone survey</td>
<td>Derived from 28-day TLFB</td>
<td></td>
</tr>
<tr>
<td>Drinking below NIAAA limits in past</td>
<td>Binary</td>
<td>Telephone survey</td>
<td>Derived from 28-day TLFB</td>
<td></td>
</tr>
<tr>
<td>28 days at 12 months follow up</td>
<td>28 days at 12 months follow up</td>
<td>TLFB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinent for past 28 days at 12 months follow up</td>
<td>Binary</td>
<td>Telephone survey</td>
<td>Derived from 28-day TLFB</td>
<td></td>
</tr>
<tr>
<td>Problem drinking at 12 months follow up</td>
<td>Continuous</td>
<td>Telephone survey</td>
<td>SIP 3 months</td>
<td></td>
</tr>
<tr>
<td>Readiness ruler</td>
<td>Continuous</td>
<td>Telephone survey</td>
<td>1-10 (0=10)</td>
<td></td>
</tr>
<tr>
<td>Importance ruler</td>
<td>Continuous</td>
<td>Telephone survey</td>
<td>1-10 (0=10)</td>
<td></td>
</tr>
<tr>
<td>Confidence ruler</td>
<td>Continuous</td>
<td>Telephone survey</td>
<td>1-10 (0=10)</td>
<td></td>
</tr>
<tr>
<td>AUDIT-C</td>
<td>Continuous</td>
<td>CDW</td>
<td>0-12 points</td>
<td></td>
</tr>
</tbody>
</table>

**C) Laboratory markers at 12 months follow up**

<table>
<thead>
<tr>
<th>Results of GGT, MCV and CDT laboratory tests at 12 months</th>
<th>Continuous</th>
<th>CPRS</th>
<th>3 lab markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal lab results for GGT, MCV, CDT</td>
<td>Binary</td>
<td>Only include if a positive trial on the primary outcomes</td>
<td></td>
</tr>
</tbody>
</table>

**D) Health-related quality of life**

<table>
<thead>
<tr>
<th>Ordinal</th>
<th>SF-12 question 1</th>
</tr>
</thead>
</table>

**E) Healthcare utilization**

<table>
<thead>
<tr>
<th>Count</th>
<th>NPCD &amp; CHARS</th>
<th>Include offset for the number of days of follow-up</th>
</tr>
</thead>
</table>

We also plan to compare the number of outpatient encounters (modeled as count data) in the intervention and control groups, over 3 months and 12 months of follow-up, stratified by department where the encounter took place: primary care, mental health care, and integrated mental health in primary care.

**Sample size**: We calculated the sample size for the proposed study in order to be well-powered to evaluate the primary outcome, which is the number of heavy drinking days (HDD) in the 28 days preceding the 12 month interview. We hypothesize that patients offered CC will have fewer HDD compared to patients who received Usual Care. We consider the minimum clinically meaningful difference to be a decrease of 4 HDD.
over a 4 week period (an average difference of 1 HDD per week) with a maximum standard deviation of 8.2-8.5. Our calculations account for potential correlation of HDD among patients with the same primary care provider by assuming a conservative intra-class correlation coefficient of 0.05 and 8 patients per primary care provider. This is conservative since previous CC trials have observed no meaningful correlation. We conservatively estimate attrition to be ≤15%, which is greater than other trials of CC for depression with assessments done by the SRP, trials of CC for depression in VA, and studies of primary care patients with AUD. To have 90% power (with a two-tailed alpha of 0.05), we require 150 patients per group for a total of 300 patients. Table 11 (above in the grant) showed that we estimate that 125 women and 971 men will be eligible and interested in enrolling in this study at the end of the Brief Telephone Screen (33%), which is a conservative estimate compared to a previous study of primary care patients with AUD. Previous AUD and CC trials have recruited more than 80% of patients at the final step of enrollment after stepped screening and consent. If we similarly recruit over 80% of eligible patients at the final step, we would enroll 100 women and 200 men. These analyses show that we have more than an adequate sample of eligible patients to achieve 90% power for Aim 1 analyses.

Randomization:

Unit of randomization (e.g., person, clinic): Person

Method used to generate the random allocation sequence): Participants allocated to the intervention groups using a computer-generated list of random numbers.

Type of randomization: Randomization was stratified by three blocking factors: site (SEA, ALVA, Other), sex, and alcohol dependence (binary). Within the 12 strata based on the 3 blocking factors, patients were randomized in permuted (variable) blocks of 6, 8, and 10 patients. The sequence of each block was kept in sealed envelopes prepared prior to recruitment.

Unit of analysis: Person

Predictor of Interest: Indicator variable for whether a person was randomized to collaborative care versus usual care (reference group), based on an intent-to-treat analysis.

Adjustment Variables:

<table>
<thead>
<tr>
<th>Covariate name</th>
<th>Data variable name</th>
<th>Type</th>
<th>Why include?</th>
<th>Data source</th>
<th>Additional details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Categorical</td>
<td>Stratification variable for randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Binary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>Binary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at baseline</td>
<td>Continuous</td>
<td>Predicts alcohol treatment engagement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HDD</td>
<td>Continuous</td>
<td>Measure of severity expected</td>
<td>Included for model of both</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Baseline values for secondary outcomes | Expected to be predictive of the follow-up measure | the HDD and the good drinking outcome (since everyone has a 9 for the good drinking outcome at baseline)

**Analysis approach:** All data collected will be screened for outliers and nonsensical values. Descriptive statistics and graphic procedures will be used to inspect distributions to ensure that they meet assumptions of statistical tests and estimation procedures. Baseline measures will be compared between CC and Usual Care groups. For each outcome, we will fit generalized estimating equations (GEE) clustered at the provider, adjusting for the variables above. Although clustering at the primary care provider-level is not expected to be clinically or statistically meaningful, we selected the GEE model in order to adjust the variance estimate for the possibility that outcomes of patients who are seen by the same providers will be correlated. The specific form of the GEE model will depend on the outcome type. For binary outcomes, binomial regression models with logit-link will be used to estimate odds ratios (ORs). For continuous outcomes linear regression models will be used to estimate mean differences; for count data, Poisson models with log-link will be used to estimate relative risks (RRs); and for ordinal variables, proportional odds models with logit-link will be used to estimate ORs. We will test the null hypothesis of no change in the outcome comparing the collaborative care group to the usual care group using a two-sided test with significance level $\alpha = 0.05$.

**Plan for handling missing data:** We will make every effort to obtain complete data on each study participant at both follow-ups, as described above. However, some missing data at follow-up is inevitable and creates a risk for selection bias that can skew results. If there is nontrivial missing data, then we plan to apply multiple imputation (MI), which assumes missing at random (MAR; i.e., that missingness depends only on observed data and not the unobserved values). We will compare results from MI to the results from a complete case analysis. We will also consider sensitivity analyses to address the possibility that the data are missing not at random (MNAR; i.e., that missingness depends on the unobserved values). To do this, we will consider a range of plausible assumptions on how the relationship between missingness and the unobserved drinking measures might differ between the control and treatment group.

**Plan for handling non-adherence to the trial protocol:** We will use an intention-to-treat analysis.

**Plan for handling multiple comparison adjustment:** Because the trial was powered based on a single outcome (HDD) and not based on a planned multiple comparison adjustment, we will not adjust for multiple comparisons in the primary analysis.
IV. REFERENCES CITED


85. McKay JR. Continuing care research: What we have learned and where we are going. J Subst Abuse Treat. 2009;36:131-145.


106. Saitz R. Linkage of Alcohol Abusers to Primary Care: 5R01AA010870-09 Boston, MA: National Institutes of Alcohol Abuse and Alcoholism; 1996.


DeBenedetti AF, Volk RJ, Kivlahan DR, Bradley KA. Using zones rather than dichotomous thresholds on the AUDIT and AUDIT-C to assess the probability of alcohol dependence. Alcoholism: Clinical and Experimental Research. 2007;31(Suppl 2: 118A (abstracts-posters)).


Achtmeyer CE, Williams EC, Kivlahan DR, Bradley KA. Clinical Reminders as research and Quality improvement tools: Lessons learned from the ADVICE trial. Paper presented at: VistA eHealth University, 2006 Nashville, TN.


management of late-life depression in the primary care setting: a randomized controlled trial. JAMA. Dec 11 2002;288(22):2836-2845.


