Web-Based Intervention to Reduce Alcohol Use in Veterans with Liver Disorders Funding Agency: VA HSR&D
Principal Investigator/Study Chair: Keith Humphreys, PhD Co-Principal Investigator: Michael Cucciare, PhD
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Abstract

As many as 80% of Veterans with the hepatitis C virus (HCV) engage in harmful drinking. This is a major health challenge given that even light and moderate alcohol consumption can worsen the course and consequences of HCV and can be a barrier to receiving antiviral therapy. In response, the VA Uniform Mental Health Services Package has made it a priority that HCV and other ambulatory clinics provide evidence-based mental health services to all Veterans engaging in harmful drinking within two weeks (but preferably the same day as the clinic visit). Our CREATE partners, the VA Office of Mental Health Services, VA Operations (10N), and the VA Office of Public Health, are strongly committed to achieving this standard throughout the Veterans Health Administration (VHA). However, the cost and organizational challenges to meeting this mandate in HCV clinics are enormous, but may be surmountable through the use of self-directed technology that minimizes demands on scarce staff time.

The primary objective of this study is to implement and evaluate a web-based brief alcohol intervention (BAI) for treating Veterans with HCV and seeking care at two VA HCV clinics - Veterans Affairs Palo Alto Health Care System (VAPAHCS) and San Francisco Veterans Affairs Medical Center (SFVAMC). This study will have three aims: First **(Aim 1)**, we plan to assess patient, provider, and system factors that may impact the initial adoption of this intervention in two VA HCV clinics. These data will result in the development of a protocol for the initial implementation of the web-based BAI at our two study sites. A secondary aim will involve obtaining patient and provider feedback on an existing web-based BAI (see www.bmi-aft.org, VA Intranet Only) to help inform its redesign for use with this population. Second **(Aim 2)**, we will implement and examine the effectiveness of a web-based BAI in two HCV clinics to reduce alcohol consumption in Veterans with HCV at three- and six-months post-treatment. Third **(Aim 3)**, we will conduct a budget impact analysis to estimate the short-term costs (1-3 years) of adoption and diffusion of the web-based BAI and the trajectory of health care spending for study participants.

List of Abbreviations

Provide a list of all abbreviations used in the protocol and their associated meanings

VHA: Veterans Health Administration

VAPAHCS: Veterans Affairs Palo Alto Health Care System
SFVAMC: San Francisco Veterans Affairs Medical Center
HCV: Hepatitis C Virus
BAI: Brief Alcohol Intervention
SUD: Substance Use Disorder
MI: Motivational Interviewing
TAU: Treatment-as-usual

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2.0 Introduction

Background and Rationale

Rates of alcohol misuse are high among individuals with HCV which can worsen health outcomes. Alcohol misuse is common among individuals with the Hepatitis C Virus (HCV) and refers to a range of consumption behaviors from risky drinking (i.e., consuming alcohol above National Institute on Alcohol Abuse and Alcoholism guidelines for daily use; NIAAA, 2011) to alcohol use disorders (Bradley et al., 2006). Prevalence rates of alcohol misuse among persons with HCV in the U.S. range from 27%-43%, while rates of HCV infection among those with an alcohol use disorder range from 18%-54% (Nguyen, Jamal, & Morgan, 2007). Alarmingly, 80% of Veterans with HCV have a history of documented alcohol abuse or dependence (El-Serag et al., 2002) which is substantially higher than in Veterans with other chronic health conditions (e.g., diabetes; Banerjea et al., 2007). Thus, it is critical to implement feasible interventions into VA HCV clinics to increase access to services that reduce alcohol consumption in this population.

Alcohol misuse can worsen HCV disease progression through at least two pathways. First, alcohol misuse is the primary cause of cirrhosis and liver transplantation in the U.S. (Hutchinson et al, 2005; Szabo, 2007; Wong et al., 2000), with even light and moderate alcohol consumption contributing to liver fibrosis in some (Monto et al., 2004). Second, alcohol consumption is a major barrier to receipt of antiviral therapy among Veterans with chronic HCV infection as any level of alcohol use may render a Veteran ineligible for antiviral therapy. For example, many VHA HCV clinics require patients to be abstinent or demonstrate substantial reductions in alcohol use for a 6-month period prior to receiving treatment (Cheung et al., 2006). Alcohol consumption may also reduce the effectiveness of antiviral therapy through biochemical and/or immune regulatory pathways (Nguyen et al., 2007; Peters & Terrault, 2002), and decrease the likelihood that patients will successfully complete a course of treatment (Anand et al., 2006). Nonadherence to antiviral therapy is particularly problematic as new, more effective treatments emerge for HCV (Jacobson et al., 2011). Therefore, alcohol misuse is an important modifiable predictor of HCV disease progression in some, as well as a common and important modifiable barrier to receipt of antiviral therapy.

Improving access to treatment for alcohol misuse is a VHA health care priority. VHA's Uniform Mental Health Services Handbook mandates that medical settings provide evidence-based assessment and treatment to Veterans with a substance use disorder (SUDs). At a minimum, VHA mandates that medical clinics (including HCV clinics) provide screening and brief intervention for Veterans engaging in harmful consumption and that this be completed within 1 to 14 days (VHA, 2008). This is particularly important for HCV clinics where alcohol misuse can interfere with treatment eligibility and potentially worsen disease progression.

Furthermore, the Uniform Mental Health Services Handbook recommends that medical clinics adopt counseling strategies based on motivational interviewing (MI) as this approach can optimize treatment engagement (OIG, 2009). Thus, it is a priority among our project partners, OMHS, Mental Health Operations (10NC), and Office of Public Health, to improve access to these services and to do so using high value strategies for reducing alcohol use among Veterans with HCV. The VA Office of Public Health has made major efforts to train providers to do BAIs face-to-face, but has found that few staff actually do so, increasing Public Health's

interest in a high value, innovative approach. Public Health is also looking for high value methods of delivering BAIs as training in face-to-face delivery of BAIs will be limited in the future due to cost concerns. Therefore, our proposed work supplements existing efforts by Public Health to increase access to alcohol treatment services within HCV clinics.

BAIs are based on the principles of motivational interviewing. BAIs refer to a range of interventions, from a single 10-minute session to multiple sessions that take place over several weeks. BAIs typically comprise two components: a brief (5-minute) assessment and personalized feedback. The assessment component collects information on frequency and quantity of alcohol use, frequency of binge drinking, potential consequences of engaging in harmful drinking patterns, and motivation (or readiness) to engage in treatment (Butler & Correia, 2009; Squires & Hester, 2004; Hester et al., 2005). The assessment data are then used to generate a personalized feedback report that provides age- and gender-matched normative comparisons of alcohol use, a description of self-reported consequences of alcohol use, and feedback on the person's degree of motivation to change alcohol or substance use (Williams et al., 2009).

BAIs that utilize web-based assessment and feedback are considered motivational interventions in that they are designed for persons who are ambivalent toward changing their alcohol use, a population which includes most individuals engaging in alcohol misuse who are not currently seeking treatment (Squires & Hester, 2004). BAIs enhance motivation to change by avoiding coercion and direct persuasion (Dunn, 2003). They instead focus on presenting information, such as negative consequences associated with harmful drinking (Vasilaki et al., 2006) and normative drinking comparisons (Williams et al., 2009), that helps build a person's own motivation to change. The information contained in personalized feedback can enhance motivation by emphasizing personal responsibility (Squires & Hester, 2004) and eliciting the person's own perceptions, values, and reasons for change (Hettema et al., 2005; Vasilaki et al., 2006).

Further, correcting misperceptions about normative drinking patterns is thought to influence alcohol use in two ways. First, an individual compares their personal alcohol consumption to normative perception about what others actually do (e.g., how much the average adult drinks). Second, the person uses their perceptions about other alcohol use as a benchmark for their own consumption patterns (Borsari & Carrey, 2001). Heavy drinkers often associate with other heavy drinkers and thus have an inaccurate perception of how much most people drink. Thus, BAIs were developed to help reveal discrepancies (a key concept in motivational interviewing; Rollnick et al., 2008) between a person's normative perceptions of alcohol use and actual consumption among age- and gender-matched peers (Hester et al., 2005; Neighbors et al., 2004; Nye et al., 1999). By correcting misperceptions about normative peer drinking behavior, personal benchmarks of "normal" alcohol use are typically reduced which thereby reduce alcohol consumption (Neighbors et al., 2004). Thus, given that BAIs are directly based on the principles of MI, they are well-positioned to support our partners in the implementation of the Uniform Mental Health Services Handbook SUD treatment guidelines which specifies a need for increased access to MI-based counseling approaches in medical settings.

BAIs are effective for civilian populations and can be delivered using various mediums. BAIs result in significant reductions in alcohol consumption among civilian adults and college students (Fleming et al., 1997; Hester et al., 2005, Kaner et al., 2007; Kypri et al., 2004; Kypri et al., 2008; Butler & Correia, 2009; Neighbors et al., 2004), with some evidence suggesting they may also be effective in active duty military populations (Williams et al., 2009). BAIs have been used to good effect in a variety of clinical settings, including primary care and HCV clinics (Dieperink, et al., 2010), For example, Dieperink et al., evaluated a face-to-face BAI delivered by HCV clinic providers and found that it reduced alcohol consumption and improved rates of antiviral treatment eligibility in a small sample (N = 47) of HCV-positive Veterans. Despite these positive outcomes, face-to-face administration of BAIs is relatively resource

intense. Some HCV clinics are unable to adopt such resource intensive treatment models and in such cases need an alternative evidence-based approach to treating alcohol misuse such as a BAI administered via the web.

BAIs can be delivered in various forms, including face-to-face (Dieperink et al., 2010) and self-administered via computer (Butler & Correia, 2009; Neighbors et al., 2004; Kypri et al., 2004), with no reduction in efficacy. Kypri et al. (2004) randomized college students presenting to a student health center to receive either a 10-15 minute web-based intervention consisting of a brief assessment of alcohol use followed by personalized feedback to education-only (i.e., information pertaining to alcohol facts and effects). Compared to the education only group, participants receiving the web-based BAI showed greater improvements in outcomes, including reductions of 26% on total ethanol consumption, 37% less episodes of heavy drinking, and 30% less alcohol-related personal problems at six-weeks post-treatment. These results are consistent with more recent studies (e.g., Kypri et al., 2008; Neighbors et al., 2004) demonstrating that web-based BAIs that incorporate brief assessment and personalized feedback are considerably more effective than education-only and produce similar sized treatment effects for alcohol consumption as those found with provider-delivered brief interventions. Despite their strong evidence base they are not always implemented because of cost and organizational challenges. Demands on staff time and clinic resources, as well as logistical barriers including disruptions in efficient clinic processes often prohibit HCV clinics from adopting provider-delivered BAIs. Thus, this study proposes a radically different approach that is easier to implement in HCV clinics and, if successful, could be disseminated by our Operational partners across VA. We will attempt to surmount the barriers posed by resource constraints, lack of staff time and interest by re-versioning, implementing, and evaluating an inexpensive, high value web-based BAI for Veterans with HCV.

Significance

Veterans with HCV report extremely high rates of current or prior alcohol use disorders (80%) and even higher than those reported in other chronically ill Veteran populations. Alcohol consumption is particularly problematic among this population as it can negatively impact eligibility for antiviral therapy and worsen HCV disease progression in some patients. Unfortunately, despite abundant data demonstrating effectiveness, person-delivered BAIs are not always implemented in HCV clinics due to many barriers (e.g., scarce provider time, limited clinic resources, and logistical concerns). As a result, there is a gap in care for HCV-positive Veterans who would likely experience improved health if they reduced or eliminated their alcohol use.

In response, VHA has highlighted the provision of screening and brief intervention for alcohol misuse in medical settings (including HCV clinics) as a national health care priority. The VHA Uniform Mental Health Services Handbook mandates that outpatient medical settings provide evidence-based screening and treatment for Veterans presenting with SUDs and do so within a relatively short time frame. The handbook also strongly recommends that clinics adopt interventions based on the principles of motivational interviewing to optimize treatment engagement. Our CREATE partners, OMHS, Mental Health Operations, and the VA Office of Public Health, are committed to meeting this health care mandate nationwide and have partnered with our project team to help re-design, implement, and test the effectiveness of low-cost, high value innovative approach to delivering BAIs in HCV clinics.

We anticipate that our study will show that web-based BAIs are a low-cost, effective, and feasible approach for reducing alcohol consumption in VA HCV clinics, and by extension could be tried in other care settings as well (e.g., surgery). We expect that participants in the web- based BAI condition will experience greater reductions in alcohol consumption frequency and quantity, and improvements in secondary outcomes such as higher rates of antiviral treatment eligibility. We also expect that Veterans in the experimental condition (web-based BAI plus treatment-as-usual [TAU]) will demonstrate increased referral and engagement to SUD

specialty care when compared to those receiving TAU only. In addition, we anticipate showing that self- directed technology can overcome traditional barriers to implementing person-delivered BAIs in HCV clinics, thereby increasing Veterans' access to these services within medical settings which is a major objective of OMHS, the VA Office of Mental Health Operations (10N), and VA Office of Public Health.

The Office of Mental Health Operation, OMHS, and the VA Office of Public Health consider this intervention affordable and scalable because of its modular and self-directed nature, and are interested in rolling it out across VA if it proves effective. Our findings will support OMHS and Mental Health Operations (10NC) in implementing the Mental Health Uniform Benefits Package by identifying an effective, low-cost intervention for treating alcohol misuse in HCV clinics. This study will also help optimize the implementation and sustained adoption of this intervention by providing our partners with (a) evidence-based recommendations for optimizing the adoption of the web-based BAI within this clinic setting, and (b) a budget impact analysis which will provide an estimate of the short-term budget implications of implementing this technology into HCV clinics nationwide. This study may also provide an alternative, evidence-based approach to treating alcohol misuse in other VA medical settings such as primary care and surgery. Furthermore, OMHS and Mental Health Operations (10NC) is interested in improving access to these services by pushing this technology to Veterans who are not yet in care and those in more rural settings. Finally, our partners find this study valuable because it enhances the link between the Office of Mental Health Services and Office of Public Health.

Population Rationale

This study will include both Veterans receiving care at VA HCV clinics and report any level of alcohol in the last 30 days and providers in VA Liver Clinics. Both men and women will be recruited. This population is critical to the study in developing a web-based BAI as a form of alcohol treatment and improving care of HCV patients. It is possible that special populations such as pregnant women, homeless, and economically or educationally disadvantaged Veterans will be eligible to participate. We will ensure that all participants understand that a decision to participate or not will not impact the services they receive at the VA. In addition, all participants will be informed that they may withdraw from participation at any time without any consequences. Informed consent will be explained in a manner that is understandable to all.

3.0 Objectives

Objectives:

The primary objective of this study is to implement and evaluate a web-based brief alcohol intervention (BAI) for treating Veterans with HCV and seeking care at two VA liver clinics - Veterans Affairs Palo Alto Health Care System (VAPAHCS) and San Francisco Veterans Affairs Medical Center (SFVAMC). This study will have three aims:

First **(Aim 1)**, we plan to assess patient, provider, and system factors that may impact the initial adoption of this intervention in two VA HCV clinics. These data will result in the development of a protocol for the initial implementation of the web-based BAI at our two study sites. A secondary aim will involve obtaining patient and provider feedback on an existing web- based BAI (see www.bmi-aft.org, VA Intranet Only) to help inform its redesign for use with this population.

Second **(Aim 2)**, we will implement and examine the effectiveness of a web-based BAI in two liver clinics to reduce alcohol consumption in Veterans with liver disease at three- and six- months post-treatment. Also, a formative evaluation will be conducted to identify potential andactual influences on the progress and effectiveness of the initial implementation efforts that may impact the likelihood that the web-based BAI will be adopted at both sites.

Third **(Aim 3)**, we will conduct a budget impact analysis to estimate the short-term costs (1-3 years) of adoption and diffusion of the web-based BAI and the trajectory of health care spending for study participants. We will estimate the budgetary impact from the VA's perspective using a one year time horizon, without discounting. We will use costs of the intervention and the subsequent health spending for participants during their enrollment in the study (six-months) and six- months after enrollment for a total of one year.

Hypotheses:

We anticipate that our study will show that web-based BAIs are a low-cost, effective, and feasible approach for reducing alcohol consumption in VA liver clinics, and by extension could be tried in other care settings as well (e.g., surgery).

Specifically, we hypothesize that compared to patients in treatment-as-usual (TAU), participants in the web-based BAI plus TAU condition will demonstrate- **H1:** greater reductions in the number of drinking days, average drinks per drinking day, and percentage of heavy drinking days; **H2:** greater improvements in health status, psychological distress, knowledge about liver disease and alcohol use, antiviral treatment eligibility, satisfaction and perceived effectiveness with treatment; and **H3:** increased utilization of VA and non-VA outpatient SUD care at three- and six-months post-treatment.

In addition, we anticipate showing that self-directed technology can overcome traditional barriers to implementing person-delivered BAIs in liver clinics, thereby increasing Veterans' access to these services within medical settings which is a major objective of OMHS, the VA Office of Mental Health Operations (10N), and VA Office of Public Health.

4.0 Resources and Personnel

This four year study will be based at two sites - the (a) VA Palo Alto Health Care System, VA HSR&D Center for Health Care Evaluation and Liver Clinic, and (b) San Francisco VA Medical Center, Liver Clinic. This study will also collaborate with the VA Women's Health Practice-Based Research Network to provide technical expertise relevant to

administrative functions (e.g., Central IRB) and enhance our team's ability to oversample for women and optimize retention of women participants in our study.

The PI, VAPAHCS and SFVAMC Co-I's, and study coordinators from each site will have access to protected health information. De-identified information will be utilized when possible in data analysis. Study coordinators at both sites, will be involved in **recruiting** subjects and obtaining **informed consent** for Aims 1 and 2 of the study. For Aim 1, study coordinators at both sites will **administer the interviews** with patients and providers. For Aim 2, the study coordinators at VAPAHCS and SFVAMC will **administer** the web-based BAI to Veterans randomized to the treatment condition at baseline, along with the assessment survey to all Veteran participants at baseline (in-person interview), and 3- and 6-months post-treatment (phone interview). **Data analysis** will be performed by the PI and Co-Is, and supported by the consultants and research staff as detailed below.

Keith N. Humphreys, Ph.D., Principal Investigator

Dr. Humphreys will oversee all aspects of the proposed project in partnership with our partners, The VA Office of Mental Health Services, Office of Mental Health Operations (10N), and VA Office of Public Health. He will supervise study personnel; coordinate data collection protocols, staff training, develop study procedures; and take responsibility for data analysis and the dissemination of findings. He will also co-lead development of the qualitative interviews and protocol, and participate in conducting interviews with staff and patients. He will ensure that the study protocol and all human subjects and data security regulations are followed. Dr.
Humphreys will also be responsible for communicating and supporting our partners in interpreting the policy and health care implications of our study findings.

Michael A. Cucciare, Ph.D.; Co-Principal Investigator – not VA Palo Alto

Dr. Cucciare's role will be to provide guidance to the study team on research methods used throughout the study, as well as on statistical analyses and interpretation. In years 1-2, Dr. Cucciare will co-lead the development of the qualitative interviews and developing recruitment protocols to be used at the VAPAHCS and SFVAMC for Aims 1 and 2. He will co-lead the development of the coding manual that will provide a framework for analyzing the de-identified content of both interviews (along with Dr. Humphreys). He will also participate in the qualitative analyses of the de-identified content (along with Drs. Cronkite and Hagedorn), and co-lead efforts to prepare reports for dissemination of findings. In years 3 and 4, Dr. Cucciare will provide guidance to the study coordinators regarding participant recruitment, study logistics and coordination at both sites, formative evaluation process (e.g., site visits, interviews with staff), follow-up interviews with participants, and database management and analysis (along with Dr. Cronkite). Dr. Cucciare will be able to access identifiable data, but it is unlikely he will need to.

Ruth Cronkite, Ph.D., Biostatistician Co-Investigator

Dr. Cronkite will be responsible for guiding the statistical and data analysis procedures, and guiding the analysis of the qualitative data.

Wei Yu, Ph.D., Health Economist Co-Investigator

Dr. Yu will direct the economic study including working with the Office of Mental Health Operations to collect VA health care utilization and cost data. He will also lead the Budget Impact Analysis of the web-based BAI. Dr. Yu will be assisted by a HERC statistical analyst at 30% FTE in year 4 and a research assistant at 20% FTE in years 1 and 4.

Ramsey Cheung, M.D. Co-Investigator
Dr. Cheung will provide expert guidance on the development of our research methodology to maximize the overall feasibility and implementability of our study protocol in the HCV clinic at the VAPAHCS. He will work alongside Dr. Humphreys and his team to champion the project with his HCV clinic colleagues and to ensure that this project receives sufficient support and access to the appropriate patient population. Dr. Cheung is an expert in the logistics of HCV clinics and will therefore provide guidance to ensure that disruptions to clinic flow will be minimized.

Alexander Monto, M.D. Co-Investigator
He will work alongside Dr. Humphreys and his team to provide guidance in implementing the web-based BAI in his clinic, ensuring that this project receives sufficient support and access to the appropriate patient population at the SFVAMC. Similar to Dr. Cheung's role, Dr. Monto will provide the study team with guidance to ensure that disruptions to clinic flow will be minimized.

Hildi Hagedorn, Ph.D. Co-Investigator- not VA Palo Alto
Dr. Hagedorn will guide the development of our research methodology including the formative evaluation plan, interpretation of the de-identified qualitative data gathered from interviews with patients and staff, site visits, and clinic observations, and structure of our hybrid type 1 design. She will also co-lead the development of our initial implementation plan, strategies for addressing barriers to the sustained adoption of the web-based BAI at both study sites, and analysis of de-identified qualitative data. Dr. Hagedorn will not have access to any identifiable information.

Steven Asch, M.D., MPH, Co-Investigator
Dr. Asch will provide guidance on the re-design of the web-based BAI (e.g., suggestions for content, strategies for integrating patient and provider feedback into the re-designed version). He will also provide guidance on developing the semi-structured interviews to be used with patients and staff working within the HCV clinic settings, and formulating an implementation plan based on obtained feedback from interviews. He will help us develop our initial implementation plan and co-develop our formative evaluation protocol. Dr. Asch will also help guide the selection of outcomes measures, data interpretation, and the dissemination of findings to our CREATE partners –VA Office of Mental Health Operations (10N), VA Office of Mental Health Services, and VA Office of Public Health.

Ann Combs, MHA, Research Health Science Specialist at VAPAHCS
Ms. Combs will serve in the role of Project Manager and study coordinator for the proposed study. She has experience managing large scale clinical trials. During the first year of the project, she will work alongside the PI and Co-Investigators to help prepare study recruitment including the development of recruitment protocols, assist with coordinating patient and provider interviews, and development of site specific Human Subjects requirements at the SFVAMC. She will also work closely with the PI and Co-Investigators to conduct qualitative interviews, work with the textual data derived from the interviews in the development of coding manuals, and applying these manuals to the interview transcripts. Upon completion of the interviews, Ms. Combs will work with the PI and the study team to coordinate the development of the re-versioned BAI with the web developer. In years 2-4, she will be responsible for recruitment, conducting follow-ups, and database management the clinical trial. In the Project Manager role, she will facilitate the information flow to the Principal and Co-Investigators and collaborate to develop and execute project goals and management plans (i.e., for recruitment, intervention delivery, and data collection at intake and follow-ups) at the VAPAHCS. She will be responsible

for assisting with administrative project oversight, such as budget, personnel, participant reimbursement, and the re-versioning of the web-based BAI. She will also work closely with the PI and Co-Investigators to provide support and necessary training to the study coordinator at the SFVAMC.

TBA, Research Health Science Specialist at SFVAMC
In years 2-4, s/he will be responsible for coordinating recruitment and conducting baseline and follow-up assessments for patients recruited from the SFVAMC HCV clinic, coordinating data collected from site visits (including but not limited to scheduling site visits and transcribing textual data collected from interviews conducted in Aim 2). S/he will also support the Project Manager in database management and meeting all VA Central and local site Human Subjects requirements.

Research Health Science Specialist, Statistical Analyst at the Health Economics Resource Center
This person will provide database management and assist Dr. Sinnott in data analyses and preparation of economic reports to the study team.

Susan Frayne, M.D., MPH, Consultant
Dr. Frayne will work with the study team in years 1 and 2 to develop recruitment protocols that help ensure the oversampling of women in the study and that promote retention of women in the study protocol. The PBRN administrative team (under the leadership of Dr. Frayne) will also provide technical expertise relevant to administrative functions, such as the Central IRB application process, OMB waiver request process, multi-site subject tracking systems, multi-site data security systems, and strategies for coordinating efforts with local clinical staff. PBRN core staff has expertise in all of these functions, and are highly qualified to assist Dr. Humphreys.

Megan Oser, Ph.D. Consultant – not VA Palo Alto
Dr. Oser has substantial expertise in the flow and logistics of VA hepatitis C clinics and will help guide the development of an initial implementation strategy, instrument selection, data analysis, and interpretation.

*** not VA Palo Alto = all non-Palo Alto or SFVA research staff will only receive de-identified data to examine in accordance with the Common Rule and HIPAA.**

5.0 Study Procedures

5.1 Study Design

Experimental Design
This mixed-methods study will utilize qualitative and quantitative methods to achieve its three primary aims. The present study will occur at two HCV clinics located at the VAPAHCS and SFVAMC. Our study sites were chosen out of concerns for cost (e.g., VA is under a tight

research funding cap) and study coordination concerns (e.g., less resources needed to manage study sites with close locations). Obviously, no two clinics in the VA system can fully represent all the realities of care and patients nationally, but it is possible to document carefully the characteristics of the selected clinics so that contextual features that may affect generalizability are known. Accordingly, we will measure both site specific and general characteristics that can be used to inform the research questions posed by each study aim. Specifically, data gathered from qualitative interviews will inform the initial implementation and re-versioning of a web- based BAI for use at both study sites. We will then use a randomized, hybrid (type 1) design with patient level clinical outcome data and formative evaluation data collected to examine the effectiveness of the web-based BAI (Curran et al., 2008) at both sites.

"Hybrid designs" integrate formative evaluation into experimental designs to identify factors that impact the effectiveness of implementation efforts (Stetler et al., 2008). Formative evaluation will be conducted and consist of site visits, clinic observations, and provider interviews to identify potential and actual influences on the progress and effectiveness of the initial implementation efforts that may impact the likelihood that the web-based BAI will be adopted at both sites.

Finally, a budget impact analysis will estimate the costs of adoption and diffusion of the BAI for Veterans with HCV and the trajectory of health care spending for these patients. We will estimate the budgetary impact from the VA's perspective using a one year time horizon, without discounting. We will use costs of the intervention and the subsequent health spending for participants during their enrollment in the study (six-months) and six- months after enrollment for a total of one year.

Aim 1 (Year 1)

To address Aim 1, we will conduct qualitative semi-structured interviews with Veterans and clinic staff at both sites to achieve two objectives: (a) identify patient, provider, and system factors that serve as potential facilitators or barriers to the initial adoption of a web-based BAI as an intervention for reducing alcohol consumption, and (b) obtain patient and provider feedback on the content and presentation of a web-based BAI to help inform its redesign for use with Veterans with HCV and consuming any level of alcohol. Re-versioning the existing intervention will increase its usefulness and adoptability among HCV providers and patients with HCV by enhancing its relevance to the specific health needs of this population. Interviews with providers and patients will be conducted over the phone.

Risks and Benefits

There are no anticipated risks associated with participation in Aim 1 of this study. However, interviews may involve risks that are currently unforeseeable. For example, it is possible that participants may experience some discomfort answering some of the questions. The benefits which may reasonably be expected to result from this study include providing the scientific community with information on HCV care and the utility of BAI in HCV clinics.

Study Population

Study coordinators at both sites will conduct semi-structured (audio-recorded) interviews, over the telephone, with both patient (N = 30, 15 per site) and provider (N=10, 5 per site) participants to help inform both the initial implementation and the re-versioning of the web-based BAI for two VA HCV clinics. Patients will include men and women veterans who have been diagnosed with HCV, attend the HCV clinic at VAPAHCS or SFVAMC, and are currently using any level of alcohol. Patients with evidence of active psychosis, dementia, and/or terminal illness will be ineligible to participate. Providers from HCV clinics at VAPAHCS or SFVAMC will be eligible to participate.

Aim 2 (Years 2-3)

Our second aim is to implement a re-versioned web-based BAI in two liver clinics and to evaluate the implementability and effectiveness of this intervention to reduce alcohol consumption in Veterans with liver disorders at three- and six-months post treatment. To achieve Aim 2, we will conduct a randomized controlled trial utilizing a hybrid (Type 1) design with patient-level clinical outcome data and formative evaluation data collected (Curran et al., 2008). Participants will be randomized to one of two treatment conditions –(a) web-based BAI plus treatment-as- usual (TAU) or (b) TAU only. We will also conduct a formative evaluation to determine the feasibility and challenges of implementing the web-based BAI into liver clinics.

Method for Randomization

We plan to use a stratified permuted block design for randomizing participants where participants are stratified by site (Palo Alto or San Francisco) and baseline severity of alcohol use (alcohol dependent, not alcohol dependent). Four randomization strata will be used: not alcohol dependent (Palo Alto), alcohol dependent (Palo Alto), not alcohol dependent (San Francisco), and alcohol dependent (San Francisco). Within each stratum, we will construct blocks of consecutive patients that vary randomly in size (either 8 or 12 participants). Each block will contain equal quantities of assignments to the two study arms arranged (permuted) in random order. A random mixture of block sizes of 8 and 12 will be used to prevent forecasting

of treatment assignments by project personnel since neither the participants nor the project staff will not be blinded to the assigned treatment condition.

Web-Based BAI Content

Participants in the experimental condition will receive a web-based BAI which follows the general approach that has proven to be effective in previous studies. The BAI consists of two components (a) a brief computerized assessment and (b) a personalized feedback report. The domains that are assessed in the BAI, and on which Veterans received personalized feedback are: (a) typical alcohol consumption; (b) lifetime negative consequences of alcohol use; (c) risk factors for unsafe drinking (e.g., combat experience, history of sexual assault, using drugs/alcohol to cope with symptoms of PTSD); (d) past 90 day use of illicit drugs, and (e) willingness to change alcohol use. Assessment information is entered into the BAI computer program directly by the patient. Our prior work demonstrated that the assessment portion of the BAI takes approximately 10-20 minutes to complete.

Once patients complete the assessment portion of the BAI, an individualized feedback report is generated for them to print out and review on their own. A study coordinator will be responsible for guiding participants through the study protocol including making sure patients print out the feedback report and answering any patient questions that might arise. The personalized feedback report was developed using the principles of motivational interviewing and consists of the following elements – a summary report of patients' weekly use of alcohol and/or other substances; normative feedback on their alcohol use with respect to their age-matched peers; estimates of the consequences of their alcohol use on their health, finances, and time spent "under the influence"; a chart indicating their peak blood alcohol content (BAC) on a day within the past 90 days when they drank the most; psychoeducation on the physiological effects of various BAC values and factors that increase/decrease BAC; social consequences of alcohol and other substance use; any reported risk factors for increasing the social/health consequences of using alcohol; and a summary of their self-reported motivation to change their alcohol consumption.

Treatment-as-Usual (TAU)

TAU in this study consists of brief education (delivered face-to-face) about the health effects of alcohol consumption on HCV disease progression (e.g., fibrosis, cirrhosis, viral load). When indicated, education is delivered by a liver clinic provider (e.g., physician assistants and mental health providers) and typically takes 5-15 minutes. This is the most commonly delivered form of TAU at both clinics. At the discretion of the assessing provider, Veterans may be encouraged to seek further assessment and treatment depending on the severity of alcohol use (e.g., abuse or dependence). These services might consist of educational classes and outpatient mental health. Participation in these services is not considered TAU and will be measured at each follow-up assessment.

Formative Evaluation Plan

We will utilize a well-established formative evaluation protocol that will include two site visits (to each study site) and interviews with staff (at each site) at three-month post initial implementation (e.g., Curran et al., 2008). This protocol will help our team identify potential and actual influences on the progress and effectiveness of the initial implementation efforts that may impact the likelihood that the web-based BAI will be implemented and sustained at both sites.

The formative evaluation will consist of two site visits in which the research team will conduct observations that will focus on clinic policies, norms, and staff-patient relationships (especially related to screening and treating current alcohol use and use of the web-based BAI).

Observations will be both formal and informal. The former will consist of "scheduled" observations where the study coordinators will observe intake interviews, screening efforts for alcohol use, educational presentations, and referral of patients reporting current alcohol use to the web-based BAI. Study staff will also perform informal observations of patient flow, and staff and staff-patient relationships in central clinic locations (e.g., nurses' station). The primary objective of these site visits is to generate written, revised summaries of clinic flow, processes for utilizing the web-based BAI, and recommendations for improving the sustained adoption of this intervention based on information collected through observations and interviews.

Risks and Benefits

There are minimal anticipated risks associated with participation in Aim 2 of this study. At the discretion of the assessing provider, Veterans indicating active alcohol consumption are most often provided education within the clinic setting about the harmful effects of alcohol on liver disorders. Therefore, the receipt of education is considered TAU in this proposed pilot study. In addition to receiving education, it is up to the discretion of the provider to recommend further assessment and treatment for the Veteran indicating active alcohol use. The decision for referral is based on the Veteran's willingness and interest in further assessment and treatment and severity of alcohol use gathered while meeting with the patient. For example, at the San Francisco liver clinic, providers may recommend patients contact outpatient mental health or seek out an educational class (e.g., one-hour educational course titled "Rethinking Drinking").

Participants randomized to the experimental condition (BAI plus TAU) will then complete the web-based BAI. They will also be asked to print out an individualized feedback report and review the report on their own (see Personalized Feedback Report sample in Appendix A). Participants randomized to the TAU only condition will complete the assessment battery and be provided a Patient Resource Sheet containing Human Subjects approved VA (e.g., Toll Free Hotline to the VA Palo Alto's Addiction Consultation and Treatment) and non-VA resources (e.g., website to Alcoholics Anonymous meeting schedule). All Veterans participating in this study will receive the Patient Resource Sheet to help encourage them to seek additional assessment and treatment.

In the event that a Veteran participant verbally expresses interest in seeking additional care to our study staff, we will arrange additional meetings between the Veteran and his/her HCV clinic provider to discuss additional treatment options. Since our team is co-located (located within the same clinic as the liver clinic providers administering the brief education), we can help facilitate this meeting in a number of ways including walking the patient back to the provider office and/or contacting the provider while the patient is completing the study to suggest further assessment and intervention. It will also be explained (by our staff) to the participant that they may (should they choose) share the contents of their individualized feedback report with any provider.

Study Population

In collaboration with our co-investigators at each study site, Dr. Ramsey Cheung (Director, VAPAHCS HCV clinic) and Dr. Alexander Monto (Director, SFVAMC HCV clinic), Veterans (N = 340) diagnosed with liver disease and currently consuming any level of alcohol will be recruited to participate. Drs. Cheung and Monto provided estimates of patient flow through each clinic per year and estimates of the percentage of patients reporting any level of alcohol consumption during their visit. Based on these estimates, we anticipate a sufficiently large patient pool from which we may recruit eligible participants. We also estimate, based on national VHA patient demographic data, that approximately 2-5% of clinic patients will be women. We will over sample for women patients in both study clinics utilizing expertise (in recruiting women for research studies) of the Practice Based Research Network (PBRN) based

at Palo Alto (under the leadership of Dr. Susan Frayne, also a consultant) and San Francisco. This will increase our ability to conduct at least exploratory, hypothesis generating sub group analysis in women.

The study sample will be drawn from a population of Veterans who currently receive VA liver clinic services. Veterans presenting to liver clinics who report engaging in any level of alcohol use within the prior 30 days will be recruited for the study. Additional criteria for inclusion include: (a) a liver disorder diagnosis, (b) not presently in treatment for a substance use disorder, and (c) no evidence of active psychosis, dementia, and/or terminal illness. The study will be conducted in liver clinics located at the VAPAHCS and SFVAMC. We estimate that we will need 170 individuals per condition at baseline for a total sample of 340 across both sites, with one half in the experimental condition and TAU condition at each site (i.e., n=85 per condition at Palo Alto, n=85 per condition at San Francisco).

For the formative evaluation, study staff will also perform informal observations of patient flow, and staff and staff-patient relationships in central clinic locations (e.g., nurses' station). Secondly, we will conduct interviews with 10 clinic staff members (5 at each study site) that help us identify possible barriers and facilitators to the sustained adoption of the web-based BAI at both study clinics. The study coordinators will conduct these interviews with providers (N = 10) following the same general recruitment and interview approach as outlined for Aim 1.

Aim 3 (Year 4)

To achieve Aim 3, the budget impact analysis will estimate the costs of adoption and diffusion of the web-based BAI for Veterans with HCV and the trajectory of health care spending for these patients. We will estimate the budgetary impact from the VA's perspective using a one year time horizon, without discounting (Mauskopf et al., 2007). We will estimate the costs of the intervention and the subsequent health spending for participants during their enrollment in the study (six months) and 6 months after enrollment for a total of 1 year. We hypothesize that the BAI intervention will increase utilization of SUD treatment in the first 6 months and then budget neutral from 6-12 months. Savings, if any, would accrue in the 6-12 months after randomization.

With consent, the study will collect the patient's social security number. We will link the social security number to the VA scrambled social security number so that we can extract their VA utilization and cost data. We will collect utilization and cost data from randomization through one year for each participant. Data will be gathered from a variety of sources.

5.2 Recruitment Methods

Aim 1

Interviews will be conducted, over the telephone, with patients (N= 30, 15 per site) and providers (N = 10, 5 per site). A rolling recruitment strategy will be used resulting in one-on-one phone interviews until enrollment is complete. Patient participants will be recruited by responding to a study flyer provided to them by their HCV clinic provider, or posted in an exam room or clinic research bulletin board. Patients may then contact us directly by a phone number listed on the study flyer. Veterans will be screened for eligibility by the study coordinators when they call in or are referred by an HCV clinic provider, and those eligible will schedule a phone interview with the research staff. Patients with evidence of active psychosis, dementia, and/or terminal illness will be ineligible to participate. Patient participants will be reimbursed $50 for their participation.

All providers working in the HCV clinics at each site will be eligible to participate in 30 minute interviews conducted over the telephone. An interdisciplinary group of 10 providers (10 at each clinic) work at each of the two HCV clinics included in our study. We will focus our efforts on recruiting a minimum of 5 providers at each site including physicians, clinic nurses (RN, LVN), and mental health staff given their involvement at different points in the screening

and intervention process. For example, within the HCV clinic setting at the Palo Alto Division of the VAPAHCS, nurses and physicians assistants are typically involved in the initial screening of alcohol use, while the mental health staff is often responsible for more in depth assessment of alcohol use, counseling, and referral. At both sites, provider participants will be recruited through clinic monthly meetings. The study coordinators, with the support of clinic Directors, will provide a short presentation on the study during clinic monthly meetings to invite providers to participate. Study coordinators will contact interested providers to schedule a thirty-minute, one- on-one semi-structured interview over the phone that will be conducted by the study coordinator. Participating clinics will be offered their choice of text books published by the American College of Physicians as a continuing medical education tool in recognition of their participation.

Aim 2

We estimate that we will need 170 individuals per condition at baseline for a total sample of 340 across both sites, with one half in the experimental condition and TAU condition at each site (i.e., n=85 per condition at Palo Alto, n=85 per condition at San Francisco).

Veterans will be recruited through provider referral, flyers posted in both liver study clinics, and through the use of administrative records (CPRS and CDW) at both sites. The PI and Co-Is will educate providers at each site about the study in their monthly meetings. Study staff will present a brief overview of the study objectives, criteria for Veteran participant eligibility, and low-response options (e.g., contacting study staff within clinic) for referring potential participants to the study. The research team will also provide flyers describing the study (e.g., describing participant eligibility and study team contact information) throughout each of the study clinics. We will place flyers in exam rooms, waiting rooms, and at clinic check-in desks. We will also provide flyers to clinic staff (e.g., nurses and mental health staff) to be given to eligible patients during the exam and subsequent psychosocial assessment.

Finally, in collaboration with our Co-Is, participants will also be recruited through the use of administrative records obtained through CPRS and CDW. Specifically, we plan to identify patients who have completed a scheduled visit during the prior week and mail them a letter (signed by the clinic director for that site) describing the study, eligibility criteria, and a phone number for contacting study staff.

Our research team has extensive experience using these recruitment strategies to good effect. For example, study Co-Principal Investigator Dr. Cucciare is currently conducting an HSR&D funded randomized clinical trial in a VA primary care clinic examining the effect of a web-based BAI on alcohol consumption among Veterans with alcohol misuse. His study is utilizing the above recruitment strategy with excellent results. For example, his [MC] study (n = 160 to date) currently has an 80% recruitment rate among eligible participants, and an 85-90% three- and six-month follow up rate (Cucciare et al., 2011). We will also take advantage of and utilize recruitment and retention strategies that are well-established among HSR&D investigators at the Center for Health Care Evaluation for use in the present study.

Patients agreeing to participate will be asked to complete an assessment at baseline and again at three- and six-months post-treatment. Baseline interviews will be conducted in person by study staff, with both follow-up assessments conducted via telephone. Participants will be reimbursed $50 (for a possible total of $100) for their participation after completion of the baseline assessment, and $25 each for the phone assessments.

Aim 3

With consent, the study will collect the patients' social security number. We will link the social security number to the VA scrambled social security number so that we can extract their

VA utilization and cost data. We will collect utilization and cost data from randomization through one year for each participant. Data will be gathered from a variety of sources.

5.3 Informed Consent Procedures

Aim 1

Informed consent will be obtained verbally over the phone by the study coordinators when patients/providers call our study team in response to a study flyer. We will request a Waiver of Documentation of Informed Consent to obtain permission from patients and providers to participate in the study and to consent to audiotaping. Informed consent will be obtained before interviews are conducted by our study staff. Patients with evidence of active psychosis, dementia, and/or terminal illness will be ineligible to participate.

Aim 2

Informed consent will be obtained in written form by the study coordinators when patients are identified as possible candidates. Patients of the liver clinic indicating any use of alcohol in the prior 30-day period will be recruited to participate in this study. To enhance the generalizability of our findings, we are only excluding Veterans who are currently enrolled in an outpatient or inpatient substance abuse program. Veteran participants currently seeking other mental health care treatment will be included in this study and the details of this care will be well documented in the baseline assessment process. This will allow us to examine whether this factor moderates the effect of the study conditions on patient outcomes. Also, patients with evidence of active psychosis, dementia, and/or terminal illness will be ineligible to participate.

Aim 3

Participants who provide informed consent for Aim 2 will also be asked for permission to use their social security numbers, which addresses data access for Aim 3.

5.4 Inclusion/Exclusion Criteria

The study sample will be drawn from a population of Veterans who currently receive VA services and providers in two VA Liver Clinics. Veterans presenting to HCV clinics who report engaging in any level of alcohol use within the prior 30 days will be recruited for the study.

Additional criteria for inclusion include: (a) a liver disease diagnosis, (b) not presently in treatment for a substance use disorder, and (c) no evidence of active psychosis, dementia, and/or terminal illness. Any provider responsible for direct patient care at either study site Liver Clinic will be eligible to participate in Aim 1.

5.5 Study Evaluations

Aim 1

Patient participants will be recruited by responding to a study flyer provided to them by their HCV clinic provider, or posted in an exam room or clinic research bulletin board. Eligible participants interested in the study will be asked their permission to be contacted by a study coordinator (who will also determine eligibility) to schedule an interview. All providers working in

the HCV clinics at each site will be eligible to participate.

Patient Interviews. The patient interviews will consist of open-ended questions, probing follow-up questions, and obtaining specific examples relevant to each CFIR domain. The interview will consist of three parts.

Part 1 will collect information on CFIR domain A –the outer and inner setting in which care occurs. Questions in this domain will collect information on the broader social and cultural context (outer) and more specific clinic processes (inner) that may affect the adoption of a web-based BAI as a potential intervention for Veterans with HCV and active alcohol use. Questions concerning the outer setting will focus on such factors as: (a) life circumstances (e.g., "To what extent do life circumstances influence your willingness to openly discuss alcohol use with your provider?") and (b) involvement/impact of other people (e.g., "How do what other people think about you affect your willingness to talk about alcohol use with your provider?",). Questions concerning the inner setting will include: (c) patient centeredness of the health care setting (e.g., "To what extent to you feel the clinic in which you receive care takes your needs and preferences into account?") and (d) access to resources (e.g., "To what extent do you feel you have access to options for supporting you in reducing your alcohol consumption?").

Part II will collect information on CFIR domain B - the characteristics of individuals involved in the care process. Questions in this domain will assess patient and provider characteristics that may influence HCV patients' willingness to discuss their alcohol use and receive care when appropriate. Example questions will focus on such factors as (e) communication (e.g., "Are there ways in which your provider talks to you that affects/influences your willingness to discuss alcohol use?"); (f) awareness of the consequences of drinking (e.g., "What do you know about alcohol's effect on your health?"); (g) importance of feedback (e.g., "What type of feedback is (or was) most influential in understanding the health effects of drinking?"); (h) decision to change(e.g., "To what extent does changing your eligibility for antiviral treatment impact you interest in seeking care for your alcohol use?"); and (i) readiness to use a web-based BAI (e.g., "Describe your degree of openness to interacting with a BAI delivered by the internet.", "What factors influence your interest/willingness to interact with a self-administered BAI?").

Part III will focus on CFIR domain C - intervention characteristics involved in the care process. Patient participants will be presented content from several evidence-based approaches for addressing alcohol use including: (a) brief advice, (b) brief alcohol counseling (e.g., VHA brief alcohol counseling performance measure), (c) brief alcohol interventions (e.g., assessment and feedback [BAI]), and (d) referral to specialty SUD care. Patient participants will be asked for feedback and reactions to the content of these care strategies, their format, and general presentation. If participants have been exposed to these approaches before in their interactions with providers, they will be asked for their reactions to and experiences with them. Patient feedback on these care strategies (and responses to questions in Parts I-II) will be used to help inform the re-versioning of the web-based BAI. For example, these interviews may yield rich information regarding patient preferences on types of specialty SUD programs (e.g., outpatient mental health) and approaches to the referral process (e.g., direct provider prescription, preference for the "hallway handoff") that will inform the manner in which we integrate this information into the web-based BAI.

Provider Interviews. Provider interviews will follow the same general strategy as the patient interviews with question development guided by both the findings of Michie et al. (2005) and Felker et al. (2006) describing factors critical in providers' adoption of innovative, evidence-based health care practices

Part 1 will consist of open-ended questions that gather information on CFIR domain A- the outer

and inner setting in which care occurs. Questions will gather data on the outer setting by examining topics such as (a) policy factors that may influence care (e.g., "How do patient/provider ratios impact your ability to provide counseling to HCV-positive patients with active alcohol use?, What impact does your clinic policy for responding to active alcohol use have on your ability to counsel HCV-positive patients?) and (b) social influences (e.g., "To what extent do social influences [peers or managers] facilitate or hinder open discussion of alcohol use with your patients?). Questions concerning the inner setting will assess such factors as (c) the clinic environment and available resources (e.g., "To what extent do physical or other resource factors facilitate or hinder your ability to have open discussions of alcohol use with your patients?") and (d) availability of time (e.g., "What preparatory steps are needed to provide effective counseling for alcohol use in this population?").

Part II will collect information on CFIR domain B - the characteristics of individuals involved in the care process, including providers' knowledge (e.g., "What do you know about the guidelines for screening and treating alcohol use in Veterans with HCV?") (f) skills (e.g., "To what extent do you feel like you have sufficient skill to identify active alcohol use with your patients?"); (g) beliefs about their own capabilities (e.g., "What do you think will happen if you provide alcohol counseling to a patient?"); (h) motivation and goals (e.g., "How much do you want to provide alcohol counseling [or referral to a web-based BAI] when indicated?"); (i) memory, attention, and decision process (e.g., "Describe any situations in which you chose not to provide alcohol counseling in response to active alcohol consumption.", "To what extent would an alternative to provider-delivered counseling, such as a self-administered BAI, help support you in addressing alcohol use in your patients?"); (j) emotions (e.g., "To what extent do emotional factors facilitate or hinder open discussion of alcohol use with your patients?") and (k) readiness to adopt a web-based BAI (e.g., "Describe your level of interest/willingness to recommend a web-based BAI to patients reporting active alcohol use." , "Describe your clinics level of readiness to adopt a web-based BAI as a potential intervention for reducing alcohol consumption".).

Part III of the interview will collect data on CFIR domain C - intervention characteristics involved in the care process. Providers will be asked to give their perceptions on current guidelines for treating alcohol use in HCV clinics and availability of treatment options at their facility. For example, potential assessment domains include: (k) perceptions about existing guidelines (e.g., "What do you think about current guidelines for addressing alcohol consumption in your clinic?" and "How effective/ineffective do you feel these guidelines are in helping you address this issue in your patient population?") and (l) perceptions about and availability of treatment options for alcohol use (e.g., "How do you feel about existing treatment options for your patients reporting active alcohol use?"). In addition, providers will be asked to provide their reactions to the following treatment options: brief physician advice, the VHA brief alcohol counseling performance measure, brief alcohol interventions (e.g., assessment and feedback [BAI]), and referral to specialty SUD care, which (along with responses to questions in Parts I-II) will inform the re-versioning of the web-based BAI.

Aim 2

Veteran participants will be randomized into the experimental condition or TAU. Participants in the experimental condition will receive a web-based BAI which follows the general approach that has proven to be effective in previous studies. The BAI consists of two components (a) a brief computerized assessment and (b) a personalized feedback report (also see section 5.1).

All participants will receive an assessment at baseline, and follow up at 3- and 6-months. The assessment consists of the following topics: demographics, liver disorder diagnosis and treatment eligibility, patient satisfaction, primary and secondary outcomes.

Assessment Instruments

(a) Demographics. Characteristic such as age, gender, and previous or current involvement with inpatient/outpatient VA (or non-VA) substance use disorder (SUD) treatment or mental health care programs will be collected from the patient and through administrative records (CPRS and CDW). We will also assess current (or past) participation in a self-help SUD program such as Alcoholics Anonymous. We will assess possible exposure to these various forms of substance abuse treatment during the three- and six-month follow up periods.

(c) Patient satisfaction. We will use a brief patient survey that we developed from our preliminary work to assess patients' satisfaction with both treatment conditions. This survey will ask patients to respond to a series of statements regarding their satisfaction with the interventions received (e.g., "I felt comfortable disclosing my alcohol use to a computer program"; "My provider helped me understand how alcohol use may worsen liver disorder(s)."). This assessment will be completed by patients upon completion of the baseline assessment (and upon completion of the web-based BAI for patients assigned to the experimental condition).

Primary Outcomes.

(d) Alcohol quantity and frequency. Reduction in alcohol use will be measured using the 30-day Time Line Follow-Back instrument (TLFB; Sobell & Sobell, 1992). The TLFB is a calendar that provides visual cues to aid persons in retrospective recall of drinking behavior. It uses "cues"(e.g., holidays, birthdays) to help a participant recall drinking behavior (e.g., frequency and quantity of alcohol use) and has been shown to be reliable and accurate when administered individually over the telephone (Sobell et al., 1996). Based on recommendations from the alcohol treatment literature we will assess the (*a) number of drinking days, (b) mean number of drinks per drinking day, and (c) percentage of heavy drinking days* in the prior 30 days as our primary outcomes (Dieperink et al., 2010; Gastfriend et al., 2007). These outcomes will be measured by comparing TLFB drinking data at baseline (30-days prior) to data collected at three- and six-month follow-up (30 days prior).

Secondary Outcomes.

(e) Consequences of alcohol use. The Short Index of Problems (SIP-3months) is a brief, 15-item version of the Drinker Inventory of Consequences (DrInC) which assesses alcohol- related problems over the prior 3-months (Woolard et al., 2004). The SIP has sound psychometric properties (Kenna et al., 2005).

(f) Symptoms of psychological distress. Symptoms of psychological distress will be measured using the Brief Symptoms Inventory (BSI). The BSI instrument provides an overview of a patient's symptoms and their intensity at a specific point in time (Derogatis & Melisaratos, 1983). The reliability, validity, and clinical utility of the BSI instrument are well-established.

(g) Health status. The Short Form-12 (SF-12) is a 12-item health survey based on the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) designed to assess two component health status summary scales (physical and mental component summaries) in the general U.S. population (Ware et al., 1996). The SF-12 has demonstrated good internal consistency reliability and construct validity (Luo et al., 2003).

(h) Seeking/receiving additional care. We will measure the degree to which Veteran participants seek additional SUD care over the course of the three- and six- month follow up periods. We will assess whether Veterans seek out outpatient/inpatient care of a substance abuse problem within or outside the VA system. We will also assess whether Veterans access self-help care outside the VA such as attending a meeting at Alcoholics Anonymous.

(i) Depressive symptoms. The Patient Health Questionnaire-9 (PHQ-9) is a 9-item depression scale based on the Diagnostic and Statistical Manual Fourth Edition (American Psychiatric Association, 2000). Items are scored (and summed) from 0 (not at all) to 3

(nearly every day), with severity of symptoms ranging from 0 to 27. The reliability and validity of the PHQ-9 are well established (Kroenke et al., 2001).

(j) Coping. The Coping Responses Inventory (CRI; Moos, 1993) will be used to assess participants' use of approach and avoidance coping strategies to manage stressful events (e.g., antiviral therapy). The CRI asks participants to identify their most significant stressor over the past 12 months, and then complete 48 items that describe specific coping strategies used to manage the stressor. Coping items are rated from 0 (not at all) to 3 (fairly often). The CRI comprises 8 subscales (e.g., problem solving) that have strong internal consistencies (Moos, 1993, 2002).

(k) Knowledge of HCV. This is a 16-item assessment of HCV knowledge based on patient education developed by the VA Hepatitis C Resource Center (2011). Total knowledge will be derived from percent of the questions answered correctly (ranging from 0 – 100%). Accuracy of HCV knowledge will be defined as percentage of correct answers with higher percentages reflecting more accurate HCV knowledge.

(l) Social norms. Two questions will assess perceived quantity and frequency of alcohol consumption among participants' peers (i.e., descriptive norms, e.g., "How many drinks on one occasion do men/women your age consume?" [frequency], while a 10-item measure will be used to assess concerns about harmful alcohol use (injunctive norms; Williams et al., 2009).

(m) Mini International Neuropsychiatric Interview (MINI). Section J, Alcohol Abuse and Dependence will measure the level of alcohol consumption over the past 30 days among participants. This is a 12-item assessment, with items rated from 0 (not at all) to 4 (extremely). This questionnaire will assess the presence of an alcohol use disorder (AUD) among participants.

Formative Evaluation Plan

We will utilize a well-established formative evaluation protocol that will include two site visits (to each study site) and interviews with staff (at each site) at three-month post initial implementation (e.g., Curran et al., 2008).

At the first site visit study staff will spend a day in each clinic reading program policy manuals and meeting with clinic directors. The latter will provide an opportunity to pose more focused questions on clinic policies (especially related to screening and treating current alcohol use). The meetings will be used to gauge clinic directors' support for the project as initial implementation will occur approximately one-year after funding notification. Therefore, it will be important to reassess clinic directors' current attitudes and beliefs, and answer any questions on the implementation process. When necessary we will provide brief, evidence summaries on the effectiveness of web-based BAIs and advocate VA practice guidelines for screening and treating alcohol use or misuse when appropriate.

For the second site visit, approximately three-months after the initial visit (and post-implementation), Co-Investigator (Asch) and site coordinator will complete a second three-day visit to each study site. This second visit will include observations of program operations and conducting interviews with clinic staff. First, we will conduct observations that will focus on clinic policies, norms, and staff-patient relationships (especially related to screening and treating current alcohol use and use of the web-based BAI). Observations will be both formal and informal. The former will consist of "scheduled" observations where the Co-I or study coordinator will observe intake interviews, screening efforts for alcohol use, educational presentations, and referral of patients reporting current alcohol use to the web-based BAI.

Study staff will also perform informal observations of patient flow, and staff and staff-patient relationships in central clinic locations (e.g., nurses' station). Second, we will conduct interviews with 10 clinic staff members (5 at each study site) that help us identify possible barriers and facilitators to the sustained adoption of the web-based BAI at both study clinics. The study coordinators will conduct these interviews with providers (N = 10) following the same general recruitment and interview approach as outlined in Aim 1.

Aim 3

With consent, the study will collect the patient's social security number. We will link the social security number to the VA scrambled social security number so that we can extract their VA utilization and cost data. We will collect utilization and cost data from randomization through one year for each participant. Data will be gathered from a variety of sources.

OMHO will provide our team with a subset of a larger OMHO global data set that includes VA SUD patient level utilization data. In doing so, they will effectively be contributing staff time of two FTE data analysts for years 3 and 4 whose job is to develop these global data sets. This contributed work overlaps existing program evaluation and quality improvement efforts regularly conducted by OMHO. This will reduce the need to pay for analysts for this project.

(a) VA Utilization Data. The Office of Mental Health Operations (OMHO) uses the VA National Patient Care Database and the Patient Treatment Files (PTF), and Decision Support System Files (DSS) to characterize quantity and type of SUD and mental health care received by individual VA patients. The OMHO databases include information on number of outpatient visits, residential care received, pharmacotherapy, psychoeducation and psychotherapy receipt, and use of detoxification services. OMHO will provide the project team with utilization data for patients included in the effectiveness study (i.e., Aim 2).

(b) VA Cost Data. Using the DSS, OMHO will provide costs associated with each of the care elements described in the utilization data sets.

(c) Non-VA Care-Utilization and Cost Data (**paid for by VA)**. Because VA patients may obtain approved health care outside the VA system during the study period, the cost of such care must be taken into account. We will use the Fee Basis file to capture all care provided outside the VA and paid for by VA.

5.6 Data Analysis

Aim 1

To address aim 1, we will conduct qualitative semi-structured (audio-recorded) interviews with both patient (N = 30, 15 per site) and provider (N=10, 5 per site) participants to help inform both the initial implementation and the re-versioning of the web-based BAI for two VA HCV clinics. Interviewing both patients and providers will allow us to better understand the patient, provider, and system factors that serve as potential facilitators
or barriers to the adoption of a web-based BAI. Sampling from both clinics will provide information on similarities and differences across both sites in HCV care and adoption of a web-based BAI.

All interviews will be audio recorded by the study coordinator. The recordings may then be sent via a secure, encrypted online server to a medical transcription company for transcribing. The transcription process will occur as soon after each interview as possible. Audio data and de-identified transcript data will be maintained on the secure server at VAPAHCS in a folder accessible only to those study staff who are involved in data processing and analysis.

Supervision and quality review of the de-identified interview notes will be provided by Dr. Cucciare and Co-Is [Drs. Hagedorn and Cronkite]. Template analysis (also known as thematic coding) will be used to identify themes in the textual data (King, 1998). The study coordinator and Co-I Dr. Cucciare will engage in the initial analysis of de-identified interview data. Following recommendations by King, the analysis process will initially be structured by the areas of content assessed in the patient and provider interviews. The study coordinator and Dr. Cucciare will consult regularly throughout data collection to discuss insights and unexpected responses from participants which may alter how some topics are addressed or how the interviews are structured.

After the interviews and transcriptions are complete, the study coordinator and Dr. Cucciare will begin developing two separate codebooks for patient and providers. Codebook development will be an iterative process. Codebooks will be initially developed based on close readings of 30% of patient (n = 9) and 40% (n = 4) of provider transcripts. Themes that emerge from the patient and provider interviews will be continuously integrated into their respective codebooks. We anticipate that the final set of themes will consist of both themes defined a priori and new themes that emerge from each set of interviews. Upon completion of the initial version of the codebooks, the study coordinator and Dr. Cucciare will discuss the application of the codebooks to each set of interviews. This process will involve practicing applying the codebooks to a single patient and provider interview. When agreement is reached, the study coordinator and Dr. Cucciare will code a random sample of 20% of patient (n = 6) and 20% of provider (n =2) interviews to establish inter rater reliability. Once reliability is established (80% agreement), we will proceed to code the remaining portion of the patient and provider transcripts. Throughout the coding process, the PI and Dr. Cucciare will regularly discuss emerging themes, changing conceptualizations of existing themes, and to prevent drift. They will also consult intermittently with the other Co-Is and consultants to discuss emerging themes and conceptualizations. After data coding is complete, data analysis will begin, focusing on the frequency of code occurrence (by participant and code) and patterns of code co-occurrence for each set of interviews.

Aim 2

Based on findings from prior studies of web-based BAIs with similar follow-up time

frames, we expect an average effect size of .35 to .40 (range is .15 to .67) on alcohol consumption outcomes in response to the web-based BAI (Kypri et al., 2004 Kypri et al., 2008 Neighbors et al., 2004). Assuming a power of 80% of detecting an effect size of .35, an alpha level of .05, a 2-tailed test, a correlation of .5 between repeated measures of an outcome variable, and a 20% attrition rate at 6 months, we estimate that we will need 170 individuals per condition at baseline for a total sample of 340 across both sites, with one half in the experimental condition and TAU condition at each site (i.e., n=85 per condition at Palo Alto, n=85 per condition at San Francisco).

Data Analysis

Prior to any regression modeling, we will first examine the sample distributions of each outcome variable and predictor variable to help us identify any possible errors in the data (e.g. coding errors). One of the benefits of our proposed use of generalized linear mixed model (GLMM) regression analyses is that is can accommodate a variety of conditional distributions for each outcome variable. Given that we will randomly assign participants to each condition, we expect the two groups to be comparable on baseline demographics and outcome variables at baseline. Nevertheless, we will conduct independent groups t-tests or chi-square analyses to check for any differences between the two groups on demographic characteristics and baseline outcome assessments. If differences are found between groups on any variables, we will control for those variables in subsequent analyses. Next, we will use generalized linear mixed-model (GLMM) regression analyses to compare the two conditions on our primary and secondary outcomes (Raudenbush et al., 2001; Singer et al., 2003). The primary hypothesis that the slope of drinking outcomes over 0 to 6 months for participants in the web-based BAI plus TAU condition will differ from the TAU only condition. We will use the repeated measures data to fit a model consisting of fixed-effect terms for time since randomization, the time by condition interaction, and the site main effect. Random intercepts will be included to account for possible correlation among repeated measurements due to patient-specific latent factors. We will examine further constraints on the covariance structure and choose the final model by assessing goodness-of-fit. We will also examine the distribution of the outcome variables and associated random error components, choose appropriate link and variance functions (McCullagh & Nelder, 1991), and review any outliers.

Examining Mediators and Moderators

Prior studies show that the effectiveness of web-based BAIs is at least partly due to the correction of misperceptions about normative alcohol use (i.e., social norms; Borsari & Carey, 2001; Neighbors et al., 2004). Therefore, we will test whether changes in social norms (e.g., descriptive and injunctive norms) mediate the effect of the web-based BAI on alcohol consumption. Following the recommendation of Baron and Kenny (1986), we will conduct a series of analytic steps (using regression models) to determine mediation: (a) we will test the effect of both intervention conditions on alcohol consumption; (b) the effect of intervention conditions on social norms; (c) the effect of social norms on alcohol consumption controlling for intervention condition; and (d) the effect of intervention condition on alcohol consumption after controlling for social norms. In addition, we will examine potential moderators (e.g., severity of alcohol use, coping, psychological distress) that may impact the effectiveness of intervention condition on treatment outcome. This analysis will help us determine whether the effectiveness of the intervention(s) is impacted by these variables at baseline and over the course of each follow-up.

Missing Data Prevention, Detection, and Adjustment

We will make every effort to prevent missing data at each assessment by achieving as high a response rate as possible. Baseline data will be collected during an in-person interview and follow-up assessments will be conducted as telephone interviews by study site

coordinators who have been trained to cover all questions and obtain as complete data as possible while respecting the patient's right to not answer specific questions. Based on previous follow-up studies of SUD patients conducted at our Center, we do not expect rates of missing data on any one variable to be greater than 5% at each assessment over and above missing data due to attrition, nor do we expect missing data to be systematically related to certain outcome variables. Nevertheless, given our plan to use an intent-to-treat approach that includes all patients who are randomized in our GLMM regression models, we will use multiple imputation. Multiple imputation procedure yields more efficient, accurate, and reliable inferences than ad- hoc methods of handling missing data (such as list wise deletion or mean substitution) (Shafer, 1997 Shafer et al., 2002; Little & Rubin, 2002).

Formative Evaluation Data Analysis

The Co-PI (Dr. Cucciare) and study coordinator will compile de-identified notes collected from observations made from both site visits to generate written summaries of clinic characteristics and pictorial descriptions of clinic processes. We will pursue a rapid analysis (e.g., Sobo et al., 2005) of interview data (collected from site visit 2) to ensure quick translation of provider feedback to actionable revisions to the initial implementation plan. The study coordinator will listen to all interview tapes within two weeks of returning from the second site visit. The Co-PI (Dr. Cucciare) and study coordinator will compile all de-identified interview and observation notes, and create barrier and facilitator tables which will be commented on and revised by the PI and Dr. Cucciare, site directors, and our Co-Is (Hagedorn, Cronkite, Asch), who are experts in qualitative analysis and implementation science. From these data we will develop barrier/facilitator summary tables to inform revisions to the initial implementation plan. These data will inform actionable next steps which include providing further education to site staff and drafting locally-customized implementation strategies (e.g., placement of the intervention within clinic, suggestions for modifying point in care in which it is utilized) (Curran et al., 2008). Upon completion of the summary tables, the study team will conduct a more comprehensive analysis of the interview tapes. Analysis of Interview data will facilitate manuscript preparation.

Aim 3

As described above, we will estimate the average cost of the intervention. For each participant, we will summarize their utilization and cost data. We will then perform a budget impact analysis of the intervention, comparing all health care costs for each arm of the study, including the costs of the intervention (e.g. providing the web-based BAI). Consistent with guidelines (Mauskopf et al., 2007), we will not include costs of developing the intervention or administrative overhead. Assuming also, that the BAI may impact both immediate decisions about alcohol use as well as decisions about other health care in the near future, we will analyze all health care utilization and costs incurred within the 12 months following randomization. We will also compare costs incurred in the first 6 months to those incurred in the second six months. We will estimate the budgetary impact for the two sites involved with the study. We will then extrapolate from these sites to create projections for other VAMCs based on the prevalence of patients with HCV and alcohol use at each site. This will allow us to estimate the budget impact of diffusing the web-based BAI throughout the VA system. Economics data will be managed in the same way as the clinical data and housed at HERC. We will adopt the same procedures and policies developed in the Aim 2.

5.7 Withdrawal of Subjects

Although we do not foresee any circumstances under which subjects will be withdrawn

from the research without their consent, there is the possibility that a participant may be deemed cognitively impaired, at which point we will withdraw them from the study. Withdrawing from the study at any point in time does not impact care or treatment at the VA.

6.1 Reporting

The Data Safety and Monitoring Plan will capture Serious Adverse Events (SAEs), i.e., death, hospitalization. It will also capture Adverse Events (AEs), i.e., suicidal or homicidal ideation, expression of severe distress, other serious psychiatric or medical symptoms. The Data Safety and Monitoring Plan will utilize the following categories in determining the severity of an event:

A. Classification of Event Severity: Events will be labeled according to severity which is based on their impact on the patient. An Event will be termed 'mild' if it does not have a major impact on the patient, 'moderate' if it causes the patient some minor inconvenience, and 'severe' if it causes a substantial disruption to the patient's well-being.

B. Event Attribution Scale: Events will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled either definitely, probably, possibly, or unrelated to the study intervention.

C. Expected Risks: This study includes no invasive procedures or medications. All changes to patients' treatment will be known to their liver care team.

We will use collected data to compare rates of SAEs between the control and intervention teams. Specifically, we will compare control and intervention serious adverse event rates and their attribution quarterly on three outcomes: Admissions for alcohol detoxification (with diagnoses), all other hospitalizations, and Deaths (with diagnosis).

In addition, we anticipate that we may encounter AEs in the following domains. These are described in greater detail below.

(1) Breach of confidentiality associated with reporting suicidal or homicidal intent to appropriate authorities or health personnel

(2) Severe distress as indicated by: (a) an increase of more than one standard deviation from their mean score on the PHQ-9 during follow-up assessments, (b) patient verbal report of a serious psychiatric distress at follow-up, (c) patients reporting significant distress due to the content of the self-report measures, or (d) patients reporting significant distress due to the content of the brief alcohol intervention. In each case, the research personnel will consult with the PI and Study Director to determine whether the participant's distress is significant enough to warrant an AE.

(3) Suicidal ideation will be indicated by: (a) self-report of significant suicidal ideation on the PHQ-9, or (b) verbal report of thoughts of suicide. Even for those who report suicidal ideation on the PHQ-9, determination of suicidality will be based on a combination of the self-report information and the interaction between the research personnel and the participant. The research personnel will be trained to identify and address suicidal ideation in patients. If the patient articulates thoughts of death or suicidal ideation, the study team member will ask the patient to elaborate on recent suicidal thoughts/behavior (e.g., does the patient have a suicide

plan). The situation will be based on the patient's responses and whether the study team member perceives that the patient is in immediate danger (e.g., an active plan verbalized). Study personnel will follow established safety protocols and contact local licensed clinical staff when appropriate. Also, the study co-PIs Dr. Humphreys and Dr. Cucciare are well- suited to manage clinical situations involving the expression of intent to harm oneself as they are both licensed clinical psychologists in the State of California

(4) Homicidal ideation will be indicated by verbal report of thoughts of hurting others in general or harming a specific individual. The study does not directly ask about homicidal ideation but this information may be provided by a participant during an interaction with study team members. This protocol will be similar to that for suicidal ideation. Specifically, the research personnel will be trained to identify and address homicidal ideation in patients. If the patient articulates thoughts of hurting others, the study team member will ask the patient to elaborate on his/her thoughts/behaviors (e.g., does the patient have a plan or specific target?). The situation will be based on the patient's responses and whether the study team member perceives that the patient or someone else is in immediate danger. Study personnel will follow established safety protocols and contact local licensed clinical staff when appropriate. Also, the study co-PIs Dr. Humphreys and Dr. Cucciare are well-suited to manage clinical situations involving the expression of intent to harm another person as they are both licensed clinical psychologists in the State of California

(5) Given the study population, it is possible that participants will report other serious psychiatric or medical symptoms. Research staff will be trained to monitor significant abnormal behavior and/or report that the patient perceives him/herself to be in imminent need of medical treatment. If it is determined that the patient requires immediate care, the research staff will coordinate access to appropriate services.

Both Dr. Humphreys and Dr. Cucciare hold Ph.D.s in clinical psychology and have treated patients who have mental health and alcohol use disorders. In the event of other forms of medical care being the subject of a patient safety decision, Dr. Humphreys will seek the advice of Co-Investigator Ramsey Cheung, M.D., Chief of Hepatology at the VA Palo Alto, Co- Investigator Alexander Monto, M.D. of the San Francisco VA and/or consultant Steven Asch, M.D. of the Palo Alto VA. All three physicians have extensive experience caring for Veterans who have liver disorders. These five project staff members will be available to consult with other project staff and/or to speak with the participant if any concerning events arise.

Triggers to action will be the participant's expression of severe distress, suicidal or homicidal ideation, and/or other serious psychiatric or medical symptoms. Research staff will be trained and prepared for situations in which a participant expresses severe distress. Specifically, all project staff will have been trained on VA's suicide risk assessment and response guidelines, including the capability of directly connecting suicidal participants to the 24-hour VA suicide hotline, as well as arranging with local psychiatry crisis management staff to assess and potentially hospitalize the patient. Subsequent to any participant's expression of severe distress, ideation, or other serious symptoms, project staff will make all reasonable attempts to re-contact the participant to monitor his or her well-being until the acute situation is resolved.

Research staff will also be trained and prepared for situations in which a participant not currently in addiction treatment reports severe alcohol misuse, e.g., a blackout, delirium tremens, alcohol-related injury). Such individuals will be protected by having project staff provide a referral to substance use disorder treatment at the VA closest to where they are residing. If the VA is rejected by the participant for any reason, project staff will utilize SAMHSA's (the federal agency within HHS that funds most non-VA substance use disorder

treatment) online substance abuse treatment facility locator to provide a referral.

7.0 Privacy and Confidentiality

We will use Protected Health Information (PHI) for this study only. PHI will not be disclosed to anyone outside of the PI, VA Palo Alto and VA San Francisco Co-Is, and research team members involved with data collection and management.

All PHI and final data collected for this study will be managed and housed at the Center for Health Care Evaluation (CHCE), located on the VA Palo Alto campus (in Menlo Park). Regarding computers and relevant technology, the CHCE has the following: a centralized server and mass data storage device that is fire-walled, encrypted, and backed-up daily; two information technology specialists to ensure data security and integrity; networked personal computers for all personnel; and statistical, publishing and database software for data management and analysis. Relevant to data storage and safety, CHCE has access to local Windows Active Directory Domain Controllers, a UNIX NIS Server and Network Appliance storage facilities. These resources allow large amounts of research data to be stored and analyzed within a secure environment, while still connected to VA computing resources. Network infrastructure and connectivity are maintained by the Shared Computer and Resources Facility (SCARF) that serves CHCE and the VA's Cooperative Studies Program Coordinating Center (CSPCC), HERC, and the Program Evaluation and Resource Center.

All PHI and related data collected for this study will be managed and housed using standard CHCE protocols for housing such data. For example, all paper and hard copy records will be kept in a locked cabinet in a locked room in building 324. Only authorized research staff will have the key to the locked cabinet. All electronic records will be kept on maintained, encrypted VA servers housed in building 324. All files and folders will be password protected. The ISO/PO will be notified within one hour if data loss or misuse is discovered.

8.0 Communication Plan

The research team will regularly meet to discuss the study's progress and address any adverse events or unanticipated issues. The study coordinators at VAPAHCS and SFVAMC will be in continuous communication as they coordinate screening and data collection and management. Both will also be in direct communication with the PI Dr. Keith Humphreys and Co-PI Dr. Michael Cucciare to remain up to date on the study protocol and to ensure that any serious adverse events or unanticipated problems are reviewed and documented appropriately. Both the PI and Co-PI (Dr. Michael Cucciare) will provide training to study staff in consent form procedures and will work with both sites to inform them of updates to the study.

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