KAISER PERMANENTE®

TITLE:

Computerized Substance Use and Depression Screening and Behavioral Treatment in HIV Primary Care

NCT NUMBER:

NCT03217058

VERSION DATE:

October 5, 2022

Research Question: What are the key barriers to implementation, factors associated with effectiveness, and cost of tablet-based screening for the continuum of SUD severity and depression, followed by BHS-delivered interventions for those who screen positive.

Aim 1. To evaluate the implementation of computerized SUD and depression screening and BHS-delivered intervention in HIV primary care.

Hypothesis 1: SUD and depression screening rates and BHS-delivered intervention will be higher in the intervention phase compared with the observation phase and will be maintained long-term.
Hypothesis 2: Greater HIV severity and younger age will increase screening rates for SUD and depression.
Hypothesis 3: More BHS-delivered intervention will occur with higher HIV, SUD and/or depression severity.

Aim 2. To examine the effectiveness of computerized screening and BHS-delivered intervention in HIV primary care among patients with moderate or high SUD risk or depression severity.

Hypothesis 1: SUD and/or psychiatry specialty care treatment initiation and antidepressant prescription use will be greater in the intervention phase compared with the observation phase.
Hypothesis 2: HIV outcomes, including ART adherence, HIV RNA control, VACS index score, and retention in HIV care will be improved in the intervention phase compared with observation phase.
Hypothesis 3: SUD and depression symptoms will decrease after implementation of the intervention.

Aim 3. To determine implementation costs and cost-effectiveness of screening and BHS-delivered intervention.

We will measure the cost per patient screened, and among those screening positive, the cost per patient initiating BHS-delivered intervention. We will also evaluate the cost-effectiveness of the intervention for achieving improvements in each HIV, SUD and depression outcome.

Aim 4: Perform key informant interviews to evaluate provider- and clinic-level implementation barriers and facilitators to computerized screening and BHS-delivered intervention.

Semi-structured interviews for selected providers and clinic staff, including qualitative and quantitative components, will be performed in each clinic.

Study Design

Description of Study Phases
Phase 1: Data only

Observational phase: The 12 months prior to implementation at each study clinic will be considered the observational phase consisting of usual care with access to specialty clinic-based SUD and depression care. Hazardous drinking screening has been implemented systematically using NIAAA guidelines,[169] along with standardized tobacco screening; both are part of the clinical workflow in the health system and are captured in the "MA Rooming Tool" used by medical assistants to capture essential preventive health measures. Screening for other substances is not standardized and instead relies on physicians' clinical practices. A combination of appointment codes and appropriate *International Classification of Diseases, (ICD) 9th and 10th edition* will be used to determine screening for alcohol and drug use. Drug use and depression data are captured in the Social History section of KP Health Connect, and will be extracted from the EHR. Treatments provided to depression patients are based on current best practices for medication management and psychotherapy.[229,230] Mild to moderate depression is often addressed in primary care with antidepressant medication, whereas patients with

more severe symptoms or complex presentations are usually referred to psychiatry clinics for specialty care. We will track these aspects of patient care in the EHR.

Phase 2: TAPS/AOQ Administration

Overview: This hybrid design intervention study will evaluate the implementation, effectiveness and cost of screening (via KP.org, tablet, or clinic-based computer during visit ["suspended hyperspace"]) for the continuum of SUD severity and depression, followed by BHS-delivered interventions for those who screen positive. The study will be performed within the 3 largest clinics in KPNC at Oakland, Sacramento and San Francisco, which collectively serve ~5,000 patients. Through this project, clinical and Division of Research staff will partner to develop and deliver patient messaging regarding SUD and depression screening. Division of Research staff will provide initial support to clinics to attach screening questionnaires to patient appointments, with the goal of transitioning this work over to clinical staff during the course of the project to inform the feasibility of long term implementation.
The study team will assist the clinics in programming computerized screening measures, contacting patients via secure message on behalf of clinicians, and training a BHS to deliver evidence-based interventions. Patients will be informed that completing the questionnaire is part of Kaiser Permanente research and completion is voluntary. This information is included in both the secure message language (for those who have KP.org) as well as in the questionnaire instructions that are displayed on the tablet or computer device during administration (see language in "Secure Message" document and "TAPS/AOQ Questionnaire").

Prior to and during routine annual HIV clinic visits, HIV patients will be asked via secure message to complete the questionnaire in KP.org. Patients who do not complete the questionnaire prior to registration in the clinic will be instructed by a receptionist to complete it on a tablet in the waiting room. Clinicians will also have an opportunity to administer the questionnaire on an as needed basis (e.g. if the tablet is unavailable) via suspended hyperspace during the clinical visit. Clinic staff will be trained by Drs. Satre and Leibowitz on questionnaire administration and interpretation. The results will be directly incorporated into the EHR and viewable by clinical staff including physicians and BHSs. Next, BHSs will review screening results and initiate MI- and CBT-based interventions as needed during the clinic visit and/or by phone. The study will employ a stepped wedge design, with implementation and effectiveness outcomes in the intervention phase compared with outcomes in the 12-month observational phase (i.e., usual care in 12 months prior to implementation). Rollout of the intervention will occur sequentially at the 3 clinics over two years (including 6-months overlap between clinics), allowing for refinement of the intervention accommodating the unique implementation challenges at each site.

The study team will assist the clinics in programming computerized screening measures, contacting patients via secure message on behalf of clinicians, and training a BHS to deliver evidence-based interventions. Prior to and during routine annual HIV clinic visits, HIV patients will be asked via secure message to complete the questionnaire in KP.org. Patients who do not complete the questionnaire prior to registration in the clinic will be instructed by a receptionist to complete it on a tablet in the waiting room. Clinicians will also have an opportunity to administer the questionnaire on an as needed basis (e.g. if the tablet is unavailable) via suspended hyperspace during the clinical visit. Clinic staff will be trained by Drs. Satre and Leibowitz on questionnaire administration and interpretation. The results will be directly incorporated into the EHR and viewable by clinical staff including physicians and BHSs. Next, BHSs will review screening results and initiate MI- and CBT-based interventions as needed during the clinic visit and/or by phone.

For more detail regarding Phase 2, see "Procedures" Section.

Study Population

Inclusion and Exclusion Criteria

Phase 1: All patients who are HIV-positive patients from the 3 largest KPNC HIV clinics at Oakland, Sacramento and San Francisco will be included in the observational phase.

Phase 2: All patients who are HIV-positive patients from the 3 largest KPNC HIV clinics at Oakland, Sacramento and San Francisco will be included in the study. There will be no additional screening for eligibility as patients will already be identified as members of the KPNC HIV registry and have a scheduled appointment with an HIV care provider at one of the participating clinics to be included.

Recruitment Methods
Phase 1: No recruitment

Phase 2: KPNC patients will not be recruited as part of this study as we propose to implement screening and treatment for SUDs and depression as part of routine HIV primary care and the implementation of the BHS intervention will be part of standard of care practices.

a. Informed Consent Process

Phase 1 (Data Only): We are requesting a Waiver of Informed consent.

Phase 2 (TAPS/AOQ Administration): We are a requesting a Waiver of Signed Informed Consent

Waiver of Informed Consent

Phase 1 (Data Only):
This study is minimal risk, The data only phase involves no active participation for patients and will be looking at retrospective data regarding access to usual care and utilization of SUD and depression care prior to the implementation of the systematized screening tool. It would be impractical to obtain informed consent from ~5,000 HIV patients who receive their routine care from one of the three participating KPNC HIV clinics.

Waiver of Signed Informed Consent

Phase 2 (TAPS/AOQ Administration):
–Condition 1 applies to our request for waiver of signed informed consent. Prior to and during routine annual HIV clinic visits, HIV patients with a KP.org account will be asked via secure message to complete the questionnaire in KP.org. The secure message will contain the elements of consent as well as a link for participants to click to complete the questionnaire. Clinicians will also have an opportunity to administer the questionnaire on an as needed basis (e.g. if the tablet is unavailable) via suspended hyperspace during the clinical visit. The elements of consent are also reiterated in the instructions displayed at the beginning of the questionnaire to ensure that patients who complete their screening via tablet or suspended hyperspace also review the necessary information and consent is assumed when patients continue to fill out the questionnaire

after reading the instructions. We are requesting a waiver of written informed consent since it would be impractical to obtain written consent from ~5,000 HIV patients who may receive the survey more than once.

In addition, we originally envisioned that clinic staff would assist with sending surveys and adding in written informed consent to the workflow would be overly burdensome to both providers and their patients. Finally, the research involves no more than minimal risk for participants as these routine, clinically important questions about substance use and mental health are already being asked by their providers in HIV clinics (with no written consent required) during their appointments..

Associates) and all PHI will be removed from transcriptions prior to data analysis. Quantitative measures will also be collected from study participants via online survey hosted by KPNC IT-approved Datstat technology. No PHI will be collected during the online survey and subjects will only be identified by their medical center (OAK, SAC, SF) and their job category (clinician, support staff, BHS, etc.).

HIPAA Privacy Rule Authorization – if study will use or disclose Protected Health Information (PHI)
Phase 1 (Data Only): We are requesting a Waiver of HIPAA Privacy Rule Authorization.

Phase 2 (TAPS/AOQ Administration): We are a requesting an Alteration of HIPAA Privacy Rule Authorization without signature.

Waiver of HIPAA Privacy Rule Authorization

Phase 1 (Data Only): The study will only recruit all adult HIV primary care patients from 1 of 3 primary HIV clinics. It is necessary to access PHI on patients including data drawn from the electronic medical record. We need to be able to link these sources of data using identifying patient information and dates of service, which includes PHI. We are requesting a waiver since it would be impractical to obtain written authorization from ~5,000 HIV patients who are eligible to participate.

Phase 2 (TAPS/AOQ Administration): We propose to implement screening and treatment for SUDs and depression as part of routine HIV primary care. Without an alteration we would be required to request signed authorization from all the clinic's patients in order to review their records. This would put an unnecessary burden on patients and would be disruptive to the clinic, due to the large number of patients who use the clinic to receive primary care. We are proposing to implement screening and treatment into routine clinical care.. In addition to the elements of consent, we will also include information regarding access to and use of PHI for this project in the secure message provided to patients who have KP.org as well as in an information sheet provided to all patients who complete the questionnaire in clinic via the tablet or suspended hyperspace function. Thus, all patients will be informed that their PHI will be accessed if they choose to participate in this project and have the opportunity to choose not to participate.

As described, the primary source of risk is potential loss of confidentiality. There is also a small risk that some patients may feel uncomfortable or experience emotional distress when answering some of the questions related to depression and thoughts of suicidality on the AOQ measure. We do not anticipate this risk is any greater than the routine care already received. Risk is further minimized by participation in the study because we will be actively monitoring TAPS/AOQ responses and providing timely notification to clinic staff for patients who endorse thoughts of self harm which may require more immediate clinical action. Under standard of care, AOQ responses that are submitted prior to visits are not flagged in such a way and a clinician may not be aware that patients endorsed thoughts of self-harm until they come in for their visit. We will also include information

regarding mental health resources to patients in both the secure message, for patients who receive the questionnaire via KP.org, as well as in the information sheet that is provided to patients who complete the questionnaire in clinic via the tablet or the suspended hyperspace feature.

Study Procedures

Phase 1: Data Only

Observational phase: The 12 months prior to implementation at each study clinic will be considered the observational phase consisting of usual care with access to specialty clinic-based SUD and depression care. Hazardous drinking screening has been implemented systematically using NIAAA guidelines,[169] along with standardized tobacco screening; both are part of the clinical workflow in the health system and are captured in the "MA Rooming Tool" used by medical assistants to capture essential preventive health measures. Screening for other substances is not standardized and instead relies on physicians' clinical practices. A combination of appointment codes and appropriate *International Classification of Diseases, (ICD) 9th and 10th edition* will be used to determine screening for alcohol and drug use. Drug use and depression data are captured in the Social History section of KP Health Connect, and will be extracted from the EHR. Treatments provided to depression patients are based on current best practices for medication management and psychotherapy. [229,230] Mild to moderate depression is often addressed in primary care with antidepressant medication, whereas patients with more severe symptoms or complex presentations are usually referred to psychiatry clinics for specialty care. We will track these aspects of patient care in the EHR.

Sleep subanalysis: We will be doing additional analysis on sleep disorders related to mental health and substance use that will require the following data: 1) patient reported outcomes on sleep, and 2) ICD9/10 codes for sleep disorders

Phase 2: TAPS/AOQ Administration

Overview: This hybrid design intervention study will evaluate the implementation, effectiveness and cost of screening (via KP.org, tablet, or clinic-based computer during visit ["suspended hyperspace"]) for the continuum of SUD severity and depression, followed by BHS-delivered interventions for those who screen positive. The study will be performed within the 3 largest clinics in KPNC at Oakland, Sacramento and San Francisco, which collectively serve ~5,000 patients. Through this project, clinical and Division of Research staff will partner to develop and deliver patient messaging regarding SUD and depression screening. Division of Research staff will provide initial support to clinics to attach screening questionnaires to patient appointments, with the goal of transitioning this work over to clinical staff during the course of the project to inform the feasibility of long term implementation.

The study team will assist the clinics in programming computerized screening measures, contacting patients via secure message on behalf of clinicians, and training a BHS to deliver evidence-based interventions. Patients will be informed that completing the questionnaire is part of Kaiser Permanente research and completion is voluntary in both the secure message language (for those who have KP.org) as well as in the questionnaire instructions that are displayed on the tablet or computer device during administration (see language in "Secure Message" document and "TAPS/AOQ Questionnaire".

Computerized patient self-administered screening measures (TAPS/AOQ). As part of annual primary care visits delivered by clinic staff, patients will complete the validated Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) tool. The taps includes 4 initial screening items asking about tobacco, alcohol,

prescription drug misuse, or other drug use in the prior 12 months; with 3 follow-up questions in each of these categories regarding substance-related problems. [J. McNeely et al., Performance of the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool for Substance Use Screening in Primary Care Patients. *Ann Intern Med.* 2016;165:690-699. doi:10.7326/M16-0317] . It is important to note that ALL HIV patients (regardless of cognitive status) are already asked questions regarding their substance use as a part of their routine clinical care, however patient responses are not documented in the health record in a consistent way across providers, which requires clinicians to look in several different areas of the health record for responses when reviewing a patient. The addition of the TAPS is an opportunity to collect substance use responses from patients in a systematic and consistent way for clinicians to refer to when reviewing patient records.

Depression measures include the PHQ-9[207], administered as part of the widely-used Kaiser Permanente Adult Outcomes Questionnaire (AOQ) that is already utilized in both electronic and paper formats for many patients throughout KPNC and procedures are already in place for clinician response to suicidal ideations indicated by patients completing the AOQ. Existing procedures will still remain in effect. Patients are routinely sent this questionnaire electronically and are told that their provider may not see the responses until the time of their appointment in the clinic. Responses to the measure are currently used as a starting point for clinicians to assess depression severity, including suicidal ideation, during clinic visits. In addition to this existing procedure, project staff will (1) include mental health resources in both the secure message as well as on the information sheet provided to patients who complete the questionnaire in clinic for patients who may experience emotional distress when answering the questions and (2) send a Staff Message to physicians when patients endorse this item on questionnaires completed prior to arrival at the clinic – so that clinic staff can respond appropriately. For example, in some cases providers may choose to reach out to a patient by phone prior to a scheduled appointment, based on their knowledge of the patient's mental health history. Thus, the proposed procedures reduce patient risk even further than standard of care administration procedures.

Automated reporting of the results of the measures into the EHR is enabled via a survey feature of KPNC's shared medical record. The generated reports, displayed in a clinical progress note, will include yes/no responses for substance use and depression, severity scores (low, medium and high risk for dependence) for each substance reported, and depression severity scores (mild, moderate, moderately severe, and severe). The intent of the screening report is to serve as a resource in the EHR for usual-care providers, a prompt for BHS providers to initiate patient outreach, and a starting point for BHSs as they conduct patient-centered clinical assessment and MI- and CBT-based intervention. Results will also be included in a new report within "iHIV", a clinical reporting tool in use at all KPNC HIV clinics and currently maintained by DOR HIV Registry staff. DOR has standard training procedures for any new iHIV users, and for assistance as needed for existing users in reviewing new reports and functionality.

Modalities of Administration: There are three modalities that will be utilized to administer the TAPS/AOQ questionnaires: 1) online via the KP.org questionnaire feature sent via secure message; 2) in clinic on a secure tablet provided by reception prior to the appointment; 3) during a clinic visit via the "suspended hyperspace" feature.

All HIV patients who have an appointment with an HIV care provider at one of the three participating KPNC clinics within two weeks will be flagged in the tracking system to have a TAPS/AOQ questionnaire attached to their upcoming visit in Health Connect. After the questionnaire is attached to the appointment, patients who have KP.org will also receive a secure message through the KP.org system with the "Secure Message" text that includes a link that allows them to complete the questionnaire prior to their appointment. Patients will receive

up to two secure messages regarding completing the questionnaire prior to their visit. Appointments scheduled within 1 week of the visit will only receive one secure message. Appointments scheduled >1 week before the visit will receive two secure messages, an initial message sent up to two weeks prior to the appointment date and an additional reminder message sent 7 days after the first message if they did not yet complete the questionnaire online. Patients who indicate to clinicians that they would no longer like to receive secure messages regarding completing the questionnaire will be flagged will no longer receive secure messages regarding completing the questionnaire prior to the appointment.

As noted above, the AOQ is already administered as standard care throughout KPNC and existing procedures are in place in the clinics for addressing patients who endorse thoughts of self harm on the measure when completing the questionnaire outside of an office visit. For patients who complete the questionnaire as part of the TAPS/AOQ prior to their appointment, these existing procedures will remain in effect and we will also minimize risk even further by adding a resource list in the secure message text for patients who may experience emotional distress when answering the questions as well as an additional level of oversight to monitor PHQ9 item responses for endorsement of "thoughts of self harm". When these results are received by study staff, a flag will occur in the tracking system and a study staff member will send a Staff Message in Health Connect within 1 business day to the clinic providers to alert them of the patient's response. Additionally, there the information sheet will be given to all patients who complete the TAPS/AOQ questionnaire in clinic to ensure that they have access to the same mental health resources as individuals who receive the questionnaire via secure message.

Patients who do not have KP.org or patients who received the secure message but did not complete the questionnaire online prior to their appointment will have a flag associated with their appointment in Health Connect which will alert reception to provide them with a tablet to complete the questionnaire when they check in prior to their visit. Patients who have a TAPS/AOQ questionnaire attached to their appointment that has not yet been completed will have a pop-up message displayed at the appointment desk. A Qx icon column AND a check-in pop-up message will display in HealthConnect. Patients who are given a tablet to complete the questionnaire in clinic will also be given an information sheet with information regarding the use of their PHI as part of this study as well as with a resources list for patients who may experience emotional distress when answering the questions. We are requesting an alteration of HIPAA Authorization for this phase of the study.

Clinicians will also have an opportunity to administer the questionnaire on an as needed basis (e.g. if the tablet is unavailable or on an ad hoc basis) via suspended hyperspace during a clinical visit. Suspended hyperspace is a feature that allows the MA or clinician to pull up the questionnaire on the computer in the exam room that allows the patient to complete the questions but restricts their access to their medical record, PHI or any other sensitive information. The questionnaire results will be directly incorporated into the EHR and viewable by clinical staff including physicians and behavioral health specialists (BHS). Next, BHSs will review screening results and initiate MI- and CBT-based interventions as needed during the clinic visit and/or by phone.

The study will employ a stepped wedge design, with implementation and effectiveness outcomes in the intervention phase compared with outcomes in the 12-month observational phase (i.e., usual care in 12 months prior to implementation). Rollout of the intervention will occur sequentially at the 3 clinics over two years (including 6-months overlap between clinics), allowing for refinement of the intervention accommodating the unique implementation challenges at each site. Patient recruitment will conclude at all three sites the end of project year 4 (7/7/2020).

Patients will only be flagged to be asked to complete the questionnaire every 6 months. Clinicians may choose to administer the questionnaire via the suspended hyperspace feature in the interim period if they deem it appropriate follow up for clinical care, however no appointment will be flagged to have a questionnaire directly attached for patient completion prior to their visit if a TAPS/AOQ has been completed within 6 months.

BHS-delivered intervention. Drs. Satre and Leibowitz will meet with clinic BHSs to introduce (or review) core cognitive behavioral therapy (CBT) - and motivational interviewing (MI)-based interventions. BHSs will be trained to review results of all computerized screenings and to provide outreach by phone[210] and/or web-based patient portal (KP.org) using secure messages. They will be coached on patient engagement and patient-centered goal setting (e.g., noting screening results but also focusing on patients' priorities and concerns), and instructed to offer individual MI/CBT sessions by phone or in person, according to clinical assessment and patient preference. MI and CBT can be effectively combined to address co-occurring depression and substance problems.[217-219] BHSs will use MI to enhance motivation to initiate specialty SUD or psychiatry treatment within KPNC for higher severity patients, which is available for all members in facilities nearby to each primary care clinic.

Intervention training. The study team will meeting with staff and providers early in the implementation phase to assist with planning for tablet or suspended hyperspace-based administration based on our prior work, e.g., work flow considerations.[91] Orientation for physicians and other providers (e.g., nurse practitioners) will include review of the new screening measures, how to locate scores in the EHR, and the BHS role in patient care and the intervention.

BHSs are Masters or Doctoral-level psychologists or licensed clinical social workers with a training foundation and experience in behavioral interventions. Currently they provide care across medical centers; and our study will support their time dedicated to HIV clinics. They often co-manage patients' medical conditions through non-pharmacologic and behavioral interventions, collaborate with primary care providers, and provide consultation to other team members in the areas of mental health, behavioral medicine, and health psychology. Dr. Satre will provide BHSs training on MI and CBT for depression and substance-use problems. Training will include 15 hours of instruction and supervised practice of brief, solution-focused, MI/CBT interventions involving 3 training cases (volunteer actors posing as patients), which is consistent with the average number of hours required for training in past clinical trials.[95]

The initial training with BHSs will also include new technology and workflow (e.g., accessing screening data and documenting encounters in the EHR), and guidelines for when to help patients initiate specialty SUD and psychiatry care (i.e., for high severity patients), suicide risk assessment, and follow-up (monitoring patient engagement and following up as needed with patient and care team to ensure linkage to treatment). Monthly consultation with Drs. Satre and Leibowitz will reinforce key clinical skills, enable clinicians to share case material and obtain feedback, and troubleshoot system and workflow challenges.

Study Timeline. This study has a 5-year timeline (**Table 2**). This will be sufficient for observation and follow-up of 4600 patients, data extraction and analysis, and interpretation and dissemination of results.

Table 2. Project Timeline

Study Activities	Year 1				Year 2				Year 3				Year 4				Year 5			
Study start up activities																				
Clinic 1 implementation																				
Clinic 2 implementation																				
Clinic 3 implementation																				
Ongoing BHS support and coaching																				
Semi-structured clinician interviews																				
One year clinic data follow up period																				
Data analysis																				
Manuscript Preparation																				
Dissemination activities																				

.

Data Sources. Study measures will be obtained from the EHR, HIV Registry, and informant interviews.

KPNC EHR. The EHR databases links information using unique member identifiers from multiple data sources including demographics, membership, ambulatory, inpatient, laboratory and prescription data. Unit costs of services obtained for each patient encounter and service are also available and can be calculated by member over time, or aggregated to physician or facility level. Vital status is captured comprehensively from member proxy reporting, deaths during a KP hospitalization, regional cancer registry vital status, quarterly Social Security Administration vital status files and death certificates. Additional detail on all EHR data sources is provided in KPNC Resources. After implementation of the intervention, results of KP.org-, tablet-, and suspended hyperspace-based SUD and depression screening during routine primary care visits will be added to the EHR.
HIV registry. The HIV registry includes all HIV patients since the early 1980s, with HIV-infection confirmed by chart review. It maintains up-to-date lists of all HIV patients, HIV transmission risk factors, dates of known HIV infection, AIDS diagnoses, and complete HIV-related lab and pharmacy data. A total of 8,186 HIV patients are current KPNC members, including 4,600 (56% of all KPNC HIV patients) from the three study clinics.

Study Measures. We will include relevant patient demographic factors in all analyses, including age, sex, race/ethnicity, and HIV risk group. Evaluating these demographics in the context of an insured population allow for the evaluation of potential disparities in screening and treatment rates, independent of differences in access to care. Other study measures for each study Aim are described below.

Aim 1 measures (implementation)

- **SUD and depression screening** during the observational phase will include EHR-based provider-documented screening for SUDs and depression. Intervention phase screening will include provider-documented screening and KP.org-, tablet-, and suspended hyperspace-based screens, also in the EHR.
- **BHS-delivered intervention** during the observational and intervention phases will be defined as one or more in-person or phone visits with a BHS. We will also measure the number of phone and in-person visits.

Aim 2 measures (effectiveness)

- **SUD and depression treatment initiation**. Patients scoring in the high SUD risk level on the TAPS or moderate to severe depression on the PHQ-9 will be encouraged to initiate specialty SUD or psychiatry treatment, and the BHS will use MI to help enhance motivation to initiate care. We will analyze SUD and depression treatment initiation rates using electronic administrative data; that is, whether the patient attended at least one in-person or phone visit with a BHS and/or in SUD or psychiatry treatment.
- **Antidepressant prescription rates**. Any prescription for antidepressants, including standard medications based on best practices guidelines in the treatment of depression.[211,230]
- **Antiretroviral (ART) medication adherence**. ART adherence will be defined using the Medication Possession Ratio (MPR)[234,235] for each ART prescribed.[236] MPR is calculated using a numerator of days' supply dispensed from first fill to end of the interval (i.e., 12 months), and a denominator of total days between first fill to end of the interval, with values ranging from 0% to 100%. Mean refill adherence will be calculated across all individual ARTs dispensed in the interval[237] distinguishing between true non-adherence or a change in ART (i.e., a new ART medication prescribed within 30 days) as in our previous work.[238] [179] .
- **HIV RNA response**. HIV RNA control, defined as undetectable HIV RNA levels below 75 copies/ml.
- **Retention in care.** We will use the Institute of Medicine's encounter-based definition of retention, defined as ≥2 HIV primary care visits within a 12-month period, ≥90 days apart.[155]
- **VACS index score**. The VACS score has been shown to correlate with mortality.[186] It incorporates 7 routinely collected clinical variables, including age, CD4, HIV RNA, hemoglobin, fibrosis index 4 (FIB-4), Hepatitis C, and

estimated glomerular filtration rate. The FIB-4 index incorporates age, platelets, and two liver function test results, including aspartate aminotransferase and alanine aminotransferase.

- **TAPS (SUD risk level) and PHQ-9** (Depression). See section **C.6.b.**

Data Analysis

Overview. The proposed study's primary aims are to examine the implementation and effectiveness and cost of computerized screening and BHS-delivered intervention. In context of the stepped wedge study design, HIV, SUD and depression outcomes will be compared between the intervention and observational phases. We will evaluate both short-term (i.e., within intervention phase) and long-term (i.e., within 1-2 years after initial intervention phase). As described in detail below, we will also employ two complementary study designs: 1) a repeated cross-section design with a different mix of individuals in each cluster (clinic) for examining implementation outcomes (e.g., Aim 1: screening rate) and 2) a cohort design for examining effectiveness in outcomes over time within the same individuals (e.g., Aim 2: retention in HIV care). Finally, we will evaluate implementation cost and cost-effectiveness, and perform qualitative interviews to assess provider- and clinic-level implementation barriers.

General Random Effects Model. Data analysis for both the cross-sectional and cohort approaches will use the random effects modeling framework which accounts for correlation between individuals within clusters and over time and is generalizable to non-normal distributions.[11] The general linear model is written as: $Y_{ijk}=m_{ij} + a_i + b_j + QX_{ij} +$
e_{ijk} where Y_{ijk} denotes the outcome for individual *k* in cluster *i* at time *j*. m_{ij} is the mean for cluster *i* at time *j*, a*i* is the random effect for cluster *i*, β_j represent fixed effect corresponding to time *j*, and X_{ij} is the treatment mode in cluster *i* at time j. α_i and ε_{ijk} are independently distributed with appropriate distributions (e.g., logistic for binary outcomes, normal for continuous outcomes) and individual level covariates (e.g., gender, age, severity) to describe mean responses may be added to this model. The underlying distribution from the model can be linked to a linear predictor by appropriate transformations (e.g. binary outcome linearized using a logit link). These models may be estimated using SAS PROC MIXED or PROC NLMIXED for normal or non-normal distributions allowing for correlation between observations and variable cluster sizes.

Aim 1. To evaluate the implementation of computerized SUD and depression screening and BHS-delivered intervention in HIV primary care. Every cluster (site) will have 4 repeated measures (at least 1 in the observation phase) and up to 3 in the intervention phase. We use screening rate to illustrate estimation and hypothesis testing ***(Aim 1, Hypothesis 1)***. Using patient-level data on screening (=1 if screened, 0 otherwise) we have a dichotomous dependent variable with patients clustered within clinics, implying correlated observations. The random effects (mixed) model framework above will be used to estimate model parameters. With the observation phase as the reference condition, we expect a significant positive coefficient associated with the indicator variable for intervention phase. We expect negative coefficients for age (implying younger individuals more likely to be screened) and CD4 count, implying those with greater HIV disease severity will be more likely to be screened ***(Aim 1, Hypothesis 2)***. We examine association between clinic factors using indicator variables for clinics since we have one clinic per intervention phase. For example, using San Francisco as the reference group, we will examine the coefficient of the indicator variables for the other facilities (e.g., OAK=1 if Oakland, 0 otherwise). The sign and magnitude of these coefficients will determine if there are clinic differences in implementation outcomes. We will replicate these analyses for examining BHS-delivered intervention among those who screen positive for SUD or depression ***(Aim 1, Hypothesis 3)***.We expect significant positive coefficients for the indicator variable for high severity indicating that more severe individuals are more likely to

receive BHS-delivered intervention than those with low or moderate severity. We will also examine the intervention's sustainability by comparing outcomes in the intervention's first and second year; a one-sided test of the coefficient of time will indicate whether outcomes were sustained in year 2.

Aim 2. To examine the effectiveness of computerized screening and BHS-delivered intervention in HIV primary care among patients with moderate or high SUD risk or depression severity. We will first compare treatment initiation in specialty clinic for those with severe SUD or depression problems and anti-depression medication prescription rates, among all patients who screen positive (**Aim 2, Hypothesis 1**). The repeated cross-section analyses will be conducted using the random effects (mixed) model framework as above with the dependent variable (whether a patient received any prescription orders initiation with SUD specialty care or Psychiatry treatment for their SUD (depression) being dichotomous. Drawing from preliminary analyses, we will include all patient-level predictors (e.g. demographics such as age and gender, severity) that are likely to be related to these outcomes. These models will use logistic regression since the outcome is dichotomous. We will use the SAS® NLMIXED or similar procedure for analyses. Sample size permitting, we will also examine the use of Buprenorphine/Naloxone for the subset of HIV patients with opioid addiction.[243,244]

We will also examine the longitudinal (cohort) effect of the intervention on clinical outcomes by comparing changes in HIV clinical parameters ***(Aim 2, Hypothesis 2)*** and SUD and depression severity ***(Aim 2, Hypothesis 3)*** for those who have return visits within the study observation period, adjusting for time between visits. We will examine changes in these values between the patient's initial screening and their subsequent visits using the random effects model described above. For example, we expect the coefficient of interest of the time x intervention variable to be positive, which would imply that BHS-delivered intervention results in greater increase in ART adherence.

Aim 3. To determine implementation costs and cost-effectiveness of screening and BHS-delivered intervention. Costs will be obtained as described in **C.8.c**. We will assess the incremental cost-effectiveness ratio as the additional cost per unit of outcome (e.g., 1% increase in mean ART adherence) between the observation and intervention phases. For example, if the BHS-delivered intervention costs $100 more per patient than during the observational phase and increases mean ART adherence from 85% to 90%, then the intervention costs $2000 per additional unit of adherence. A cost-effectiveness acceptability curve will be obtained from the distribution of the ICER which will be constructed using the bootstrap method based on the variances of estimates of costs and effectiveness as we have done in prior work.[166] This can be used by policy-makers to determine potential gain in effectiveness for acceptable cost thresholds.