LEVERAGING TECHNOLOGY TO ADDRESS UNHEALTHY DRUG USE IN PRIMARY CARE SETTINGS
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1. Purpose of the Study and Background

The proposed study involves developing and testing a computer-assisted approach to delivery of screening and brief interventions, using a 'Substance Use Screening and Intervention Tool (SUSIT)' in primary care patients. Our central hypothesis is that introducing the SUSIT will facilitate the integration of substance use screening and interventions into primary medical care, resulting in higher rates of brief intervention by primary care providers and lower rates of unhealthy drug use in patients who receive the SUSIT intervention, as opposed to screening only. We propose to develop clinical decision support (CDS) and then test the full SUSIT model, incorporated into primary care medical visits. A mixed methods approach will assess its acceptability and adoption among providers and patients, and gather preliminary data on its efficacy for reducing 'moderate-risk' drug use (defined as unhealthy use that is below the threshold of a substance use disorder). In the main study period, a pre-post design will ascertain the dose of substance use intervention received and changes in drug use among patients with moderate-risk drug use enrolled in the screening only (SO) versus SUSIT intervention period (n=75 in each period).

1.1. Specific aims

This study has 3 specific aims:
Aim 1 is to develop clinical decision support that assists primary care providers in carrying out a brief intervention.
Aim 2 is to assess the impact of the SUSIT on dose of substance use brief intervention received by patients.
Aim 3 is to gather preliminary evidence on the efficacy of the SUSIT approach for reducing moderate-risk drug use.

1.2. Background

Substance use accounts for more morbidity, mortality, and disability than any other preventable condition.[1, 2] While the vast majority of unhealthy substance use is not severe enough to rise to the threshold of a substance use disorder,[3] it nonetheless confers a significant burden of health risk. Individuals with 'moderate-risk' use, who use drugs or alcohol at hazardous levels but have not developed dependence or severe problems related to use, are at elevated risk for developing a substance use disorder and for experiencing negative health effects including overdose death, traumatic injury, direct health effects of substance use, and poor treatment of other medical conditions.[4-8] These individuals rarely receive assistance, because substance use is not addressed in general health care settings, and addiction treatment programs serve only those with more severe disorders. Screening, brief intervention, and referral to treatment (SBIRT) programs have been advanced as a strategy for addressing the gap in services for early identification and intervention, but these programs have been difficult to implement and sustain, and have not proven efficacious for reducing drug use.[9]

There is an urgent need to examine new models of care that could effectively address unhealthy drug use in primary care settings. SBIRT studies have tested a 'specialist' model, which shifts the responsibility for screening and interventions onto a specialized health educator who is not part of the regular primary care team. An alternative model, which integrates screening and interventions into regular primary care, using the same approaches that are effective for other common chronic health conditions, may be more effective for reducing unhealthy drug use. Innovative application of health information technology can overcome barriers to implementing a primary care-integrated approach.

The significance of our proposal is that it develops and tests an alternative model that fully integrates screening and interventions for unhealthy drug use into regular primary care services. By taking full

advantage of the existing therapeutic relationship and clinical interactions between the patient and their PCP, a primary care-integrated approach should have greater efficacy for reducing unhealthy drug use. Research on behavioral health treatment in primary care has clearly established that primary care provider involvement is a key component of effective interventions. Studies on alcohol and tobacco interventions show that PCP-provided counseling is more effective than that delivered by other care providers.[10-12] The PCP is at the center of evidence-based approaches to chronic disease management in primary care, including collaborative care models for treatment of depression.[13-17] The importance of the PCP-patient relationship appears to hold true for drug interventions as well; preliminary results from a study testing a model in which PCPs participated in the brief intervention demonstrated reduced drug use at 3 months.[18]

A primary care-integrated approach to addressing unhealthy drug use has not been adopted due to implementation barriers, the most prominent of which are the time and knowledge required to screen, conduct a clinical assessment, and deliver a brief intervention during the medical visit. Innovative application of existing health information technology can overcome these barriers. The three elements of our Substance Use Screening and Intervention Tool (SUSIT) are designed to facilitate a primary care-integrated approach to substance use intervention. 1) Time and workflow constraints are addressed with patient self-administered screening completed before the clinical encounter, with results presented to the primary care provider at the point of care. 2) Clinical decision support (CDS) assists the primary care provider in carrying out a brief intervention, while 3) clinical reminders at each follow-up visit prompt PCPs to address drug use in a longitudinal fashion. These features facilitate implementation and support effective clinical intervention in the context of the medical visit.

Substance Use Screening and Intervention Tool (SUSIT)
1. Self-administered screening
2. Clinical decision support
3. Clinical reminders

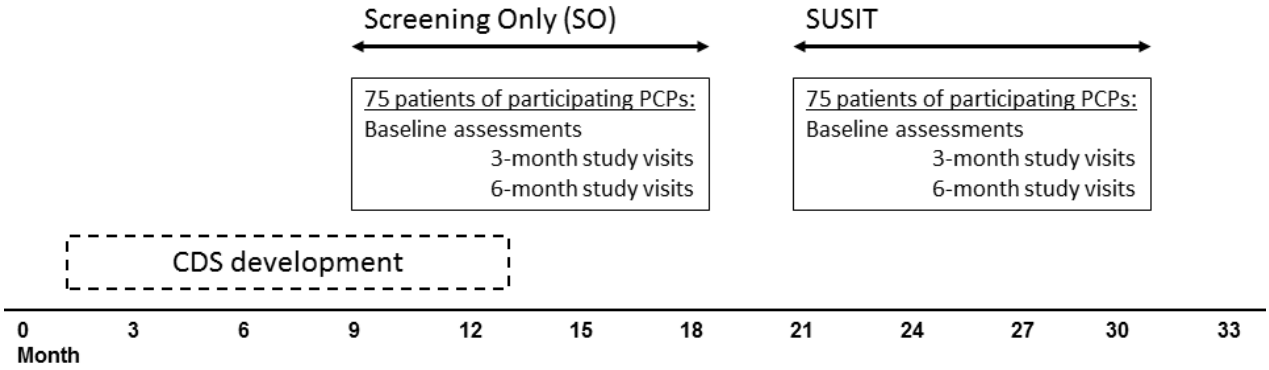
The SUSIT screener consists of the Substance Use Brief Screen (SUBS), followed by the ACASI ASSIST. Dr. McNeely's K23 research established the SUBS and ACASI ASSIST as reliable and accurate self-administered screening tools that are brief enough for use in primary care settings, and well accepted by patients.[19-22] The 4-item SUBS identifies past-year unhealthy use of tobacco, alcohol, illicit drugs, and non-medical use of prescription drugs. The SUBS was validated in 586 adult patients from two urban safety-net primary care clinics,[19] and demonstrated good sensitivity and specificity for detection of past year unhealthy use of tobacco (sensitivity 98%, specificity 96%, AUC 0.97); alcohol (sensitivity 85%, specificity 77%, AUC 0.81); and drugs (sensitivity 83%, specificity 91%, AUC 0.87 for illicit or prescription drug use). The ACASI ASSIST was modified from the WHO Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[23] to integrate items on prescription drug misuse (stimulants, opioids) and to be delivered as an audio computer-assisted self-interview (ACASI). In the TEST screening approach, the ACASI ASSIST functions as a brief structured assessment that flows seamlessly from the SUBS, to collect substance-specific information about what drugs are used and risk level (low, moderate, high). In the validation study (N=393),[24] ACASI ASSIST scores were highly correlated with those from the reference standard interviewer-administered ASSIST (ICC=0.94 for global ASSIST score).[20] The ACASI ASSIST was feasible even in a study population with relatively low levels of education: 5% required assistance, and median completion time was 3.7 minutes (range 0.7-15.4). Qualitative interviews and surveys indicated that the ACASI ASSIST was well accepted by patients: 27% preferred the computer over an interviewer, while 58% had no preference.[24]

1.3. Study design

The proposed study will develop (in Phase 1) a clinical decision support tool that assists primacy care providers in carrying out substance use interventions, and then compare (in Phase 2) two

received, and changes in drug use at 3 and 6 months, among primary care patients. We will develop the CDS component and then test the full SUSIT approach, using mixed methods to assess its acceptability and adoption, and gathering preliminary data on its efficacy for reducing unhealthy drug use. CDS development is concurrent with the SO phase to avoid losing valuable time, but will be conducted at a secondary study site to avoid contaminating the SO condition. In each treatment condition we will enroll 75 patients with moderate-risk drug use, who present for a medical visit with one of ten PCPs (Figure 1). A pre-post design will ascertain the dose of substance use intervention received and changes in drug use among patients enrolled in the screening only (SO) versus SUSIT intervention period.

Figure 1: Study design



2. Characteristics of the research population

Main study sites: Bellevue Hospital Center (BHC) and Gouveneur Health will serve as the main study sites. Both sites serve a diverse and medically underserved population. The proposed study will recruit patients and primary care providers (PCPs) from the adult primary care clinics and the virology clinic at Bellevue Hospital Center. Up to 265 participants will be enrolled in the study. In Phase 1, up to 50 patients from Gouverneur Health and 35 PCPs from Bellevue and Gouverneur will participate in CDS development. In Phase 2, 150 patients and up to 30 PCPs from all study sites will participate.

Enrollment only sites: Two additional clinics are enrollment only sites, with limited study activities, in Phase 2 only. The enrollment only sites are two HIV clinics that function as primary care clinics. These sites are located at Lincoln Hospital in the Bronx, and Kings County Hospital in Brooklyn, Including these sites in the study offers an opportunity to understand the feasibility and impact of the SUSIT approach in a larger and more geographically diverse population of HIV primary care patients, but does not change the overall study aims or design. Enrollment only sites will have the same inclusion and exclusion criteria. The patients and PCPs from these sites are included in the overall limit (maximum 150 patients and 30 PCPs in Phase 2) for enrollment across all study sites.

2.1. Demographic characteristics

Race/Ethnicity and Gender: We anticipate that study participants will reflect the gender and racial characteristics of the participating clinic(s). Forty-five percent of Bellevue patients are of Hispanic ethnicity (representing many countries), 40% are African American (including Caribbean and African immigrants), and 10% are Asian American. No one will be excluded from participation on the basis of gender, race, or ethnicity.

Age: Study participants will be adults 18 years of age and older.

2.2. Inclusion and exclusion criteria

Primary Care Providers: Up to 65 PCPs are anticipated to participate in the study. In Phase 1, up to 35 PCPs from Gouverneur Health and Bellevue will participate in content development, usability testing and clinical testing of the clinical decision support tool. In Phase 2, up to 30 PCPs from Bellevue Hospital will participate. Participating PCPs can be medical doctors (MDs), doctors of osteopathic medicine (DOs), nurse practitioners (NPs), or physician assistants (PAs). Medical students and residents are not included. There are no additional eligibility or exclusion criteria for providers.

Patients: Up to 200 patients are anticipated to participate (50 in Phase 1, and 150 in Phase 2). Patients are recruited if they have a medical visit with one of the participating PCPs. Because the SUSIT self-administered screening instrument is currently available in English and Spanish, the study is restricted to English and Spanish speaking patients.
Inclusion criteria:

- Substance use screening results (collected using the tablet-based screening tool) indicating current moderate risk drug use, based on a substance specific involvement score (SSIS) indicating current (past 3 months) use of at least one drug with a moderate risk level (SSIS 4-26), in the absence of any high-risk drug or alcohol use (SSIS 27+);
- 18 years or older;
- English and Spanish speaking;
- Presenting for visit with a participating PCP; and
- Able to provide informed consent
- Available to complete two follow up visits (3 months and 6 months after baseline appointment)

Exclusion criteria:

- Prior participation in the study (i.e. participation in the SO study phase would preclude participation in the SUSIT phase);
- Attending a formal addiction treatment program (not including informal treatment such as Alcoholics Anonymous, Narcotics Anonymous), in the past 3 months;
- Pregnant (based on self-report).
- Unable to read text on the tablet-based screening tool, or physically unable to operate the tablet.

The PI's prior study in this clinic indicates that 17% of all patients will meet eligibility criteria.

2.3. Vulnerable subjects

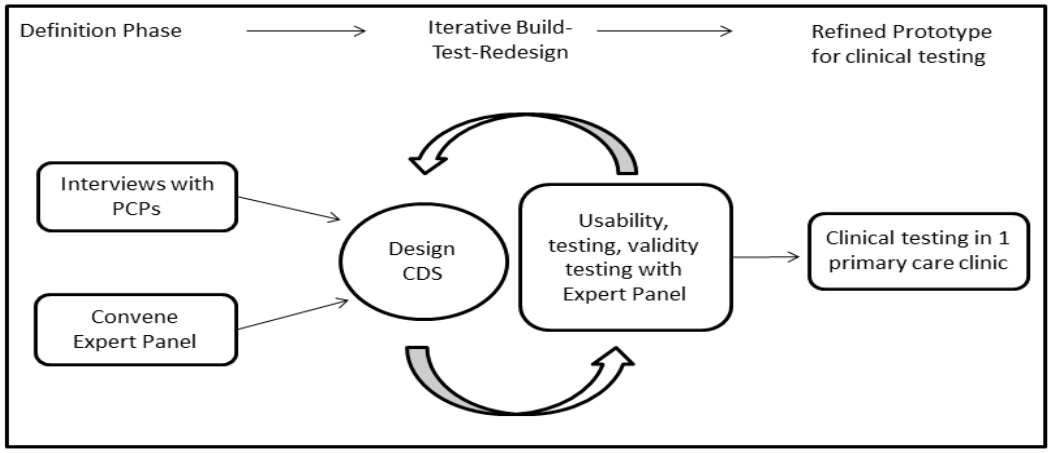
The study will not enroll high-risk drug and alcohol users because a preponderance of evidence indicates that brief intervention alone is not sufficient to address severe (high-risk, dependent) substance use. While primary care-based pharmacotherapy can be effective for drug and alcohol dependence, these more intensive interventions are out of the scope of the proposed study. Pregnant women are excluded because the potential risks to the fetus of ongoing drug use changes the threshold for intervention, may alter the motivation of the patient to change their use, and can hinder follow-up at 6 months. We will offer treatment referrals to high-risk and pregnant patients, as detailed in section 4.3. No other vulnerable populations are enrolled.

3. Methods and procedures

3.1. Study conditions, methods, and procedures

3.1.a.Phase 1: Development of CDS:
We will develop the CDS using accepted best practices,[25-28] and conduct usability testing of the SUSIT CDS tool following a standard and widely adopted approach.[29] This is a 3-phase process consisting of definition, usability testing, and clinical testing, as portrayed in Figure 2.

Figure 2: Procedure for developing CDS



Definition of the CDS tool consists of specifying the basic content of the brief intervention and soliciting the opinions of practicing PCPs and an expert panel on clinical information requirements and design preferences. The expert panel will include nationally recognized HIT experts as well as a medical director and two primary care providers from the participating study sites. Structure of the CDS is based on the Brief Negotiated Interview (BNI),[30] which assists providers in conducting a brief (3-5 minute) intervention by guiding them through the four major components of a brief negotiated interview: raising the subject, providing feedback, enhancing motivation, and negotiating a plan.

As an initial step in content development, semi-structured interviews will be conducted with a purposively selected sample of 5 PCPs from the Bellevue site. Interviews will elucidate the design elements most likely to impact 'perceived usefulness' and 'perceived ease of use' of the CDS component. Recommendations of PCPs and the expert panel will be reviewed by the investigators, and then incorporated by the software development team into a CDS prototype. The prototype design will follow accepted best practices for CDS, as defined by a growing body of heuristics developed for displaying guideline information for different types of systems and disease areas (that have emerged from systematic reviews and usability engineering).[25-28, 31-34]

Usability testing: The prototype CDS will be tested by PCP end-users recruited from Gouverneur Health, and Bellevue Hospital Center. Users will be given simulated clinical scenarios and asked to 'think-aloud' while interacting with the CDS. The user's interaction with the CDS will be recorded in its entirety by video screen recording software (capturing their computer screen, with no image of the participant), and digital audio recording. This data will be analyzed to identify usability issues and areas for potential optimization. We plan 3 cycles of usability testing.

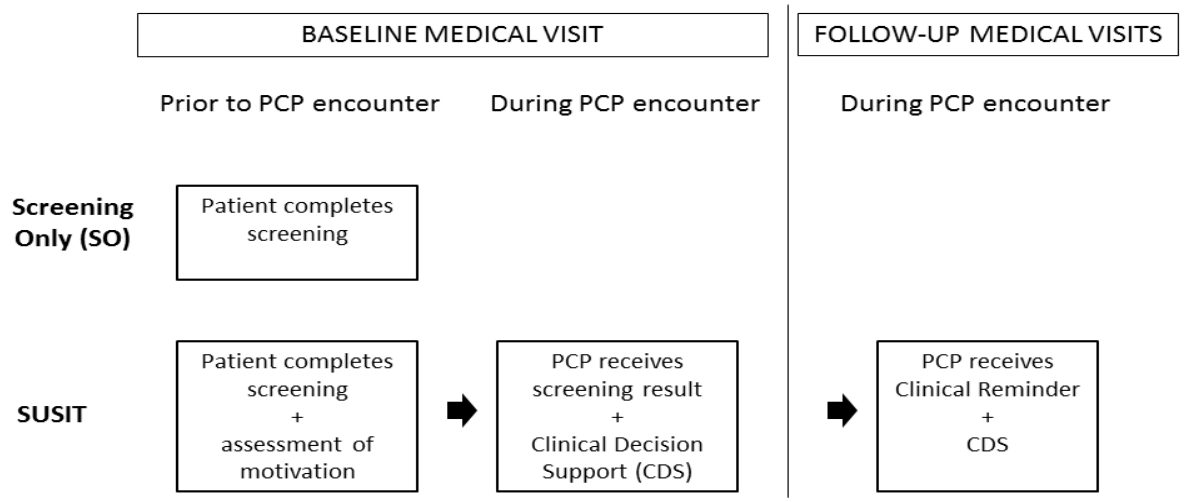
Clinical testing: A refined prototype will then be tested in clinical practice by 5 PCPs. PCPs will be asked to use the CDS in their regular practice for 2 weeks, at the end of which they will participate in a semi-structured interview with the PI and will complete a structured questionnaire (modified TAM2) that gathers information on their attitudes and experiences with using the tool. Up to 45 patients will be recruited and enrolled following the procedures detailed in Section 5, and PCPs will be provided with screening results for those with moderate-risk drug use.

3.1.b.Phase 2: Screening Only (SO) vs. SUSIT

Phase 2 is conducted at Bellevue Hospital's Adult Primary Care Clinic and Virology Clinic. Adult patients of the participating PCPs will be recruited and enrolled following the procedures detailed in Section 5. The participating PCPs will receive screening results, CDS, and clinical reminders during the SUSIT condition, to help them address unhealthy drug use in their patients. The intervention that patients receive is determined by the period in which they are enrolled (i.e. Screening Only (SO)

vs. SUSIT), as indicated in Figure 3.Participating patients in both the SO and the SUSIT condition will enter responses to the tablet computer self-administered substance use screening tool. Screening is self- administered using a touch-screen tablet, and completed by patients in the waiting area prior to the clinical encounter. Substance use screening is part of a brief 'healthy lifestyle survey,' which also includes items on diet and exercise adapted from an existing health risk assessment.[35] After the baseline medical encounter, patients will provide verbal responses to structured interviews. They will also complete a demographics form, and a self-administered computerized exit survey to ascertain whether their PCP provided elements of a substance use brief intervention during the medical visit, and various assessments described below. The exit survey will be administered again at any follow- up medical visits with the PCP that occur during the study period.

Figure 3. Study conditions



Screening Only (SO) condition: Patient and PCP are not presented with screening results. The PCP does not receive clinical decision support, or clinical reminders.

SUSIT condition: Following completion of substance use screening, the tablet computer presents screening results (including level of risk) to the patient for each substance used, asks them to identify their drug of most concern (DOMC), and assesses readiness and confidence to change behavior. Results are delivered to the PCP at the point of care, paired with clinical decision support tailored to the patient's screening results. This information is delivered on the tablet computer, which is handed to the PCP by a Medical Assistant. CDS guides the PCP through a brief intervention specific to the DOMC, recommends clinical actions pertaining to the substance and risk level, and generates a printed summary for the patient. At each scheduled follow-up medical visit, the PCP receives a clinical reminder containing a summary of the patient's substance use and level of risk, paired with CDS that guides them through a follow-up brief intervention. A member of the study team will call, email, or text patients prior to these scheduled follow-up medical visits, to confirm that they will be attending.

Phase 2 SUSIT Condition at Enrollment Only Sites: Enrollment only sites will participate only in the Phase 2 SUSIT condition. All research activity at these sites is conducted by NYU Research Staff. The NYU research staff will obtain consent and enroll study participants (including both PCPs and patients), and only those individuals who give consent for participation will have any involvement with the study at these sites. After obtaining consent, the NYU research staff will conduct assessments

with enrolled patients at the baseline, 3 month, and 6 month study visits.

Patient participant assessments in SO and SUSIT conditions (Table 1)
In both the SO and SUSIT conditions, study visits are at baseline (same day as the primary care visit), 3 months, and 6 months. Exit surveys ascertain what elements of brief intervention were conducted by the PCP, and are conducted at the baseline visit, the 3 month, the 6 month and at each follow-up medical visit. If the patient has not seen their provider in the last 3 months, they will not have to complete the survey. To minimize any potential for the RA to influence reporting, patients will self-administer the exit survey, prior to collection of additional substance use measures. PCPs will receive a clinical reminder for patients in the SUSIT condition, and may consequently address substance use
differently than in the SO condition. For this reason, we will record scheduled follow-up medical appointments, and call, email or text participants several days prior to appointments.

At the baseline study visit, and at the 3- and 6-month study visits, the RA will administer substance use assessments: Timeline follow-back (TLFB),[36] Composite International Diagnostic Interview, Second Edition, Substance Abuse Module (CIDI-SAM),[37-41] for Spanish speaking patients the M.I.N.I (Mini-International Neuropsychiatric Interview) will be used as the measure of substance use disorder, because the CIDI is not currently available in Spanish, the Short Inventory of Problems for alcohol and drugs (SIP and SIP-DU),[42] the first 8 items of the Patient Health Questionnaire (PHQ-8), and the Generalized Anxiety Disorder 7-item scale (GAD-7).Participants will provide hair samples for drug toxicology testing at the month-6 study visit. This will detect common drugs of abuse, as a means of corroborating self-report of recent drug use. If after repeated outreach attempts, and the participant is still not able to meet with RA in person, a phone interview will be scheduled with the participant for either the 3 or 6 month follow-up interview. This will be a one-to-one phone interview, with the RA or RC (whomever is conducting the interview) will be a private area. When scheduling the phone interview will ask the participant to ensure being in private space during the phone interview. For those participants that will have their 6 month interview by phone, the hair sample will become not applicable for those participants.

Chart review: Research staff will perform a structured chart review of the participant's medical record that examines the content of notes written by the participant's primary care provider(s) during the 12 months following study enrollment (inclusive of the data of enrollment). The chart review collects similar information to the patient exit survey; namely, documentation of any discussion by the primary care provider about drug, tobacco, or alcohol use. The chart abstraction form will be approved by the IRB.

Individual in-depth interviews with patient participants will characterize the acceptability to patients of conducting substance use screening and interventions in primary care. A purposive sampling approach will be used to select 12 patients who are already enrolled in the SO or SUSIT arm of the study. Those selected will represent a range of sex and age groups. The attitudes of patients are particularly important when addressing a stigmatized behavior such as substance use. While self-administered screening tools may allow for more honest reporting of stigmatizing behaviors,[43-46] some patients might prefer face-to-face communication with their providers.

Table 1. Phase 2 Outcomes and measures

Outcome	**Measures**	**Source**	**Collected at**
Primary Outcome:			

Patient receipt of a substance use intervention	Audio recordings of medical visits, transcribed and coded with BAS scale	Audio recording of medical visit	Baseline and all follow-up PCP visits (SUSIT condition only)
	Patient exit survey: -Frequency of intervention -Elements of intervention	Patient (self-administered)	Baseline and all follow-up PCP visits
	Chart review -Frequency of intervention -Elements of intervention	Medical Record	Baseline and all follow-up PCP visits
Secondary Outcomes:			
Disclosure of substance use on screening	ACASI ASSIST vs. TLFB and hair test results	Patient	Baseline 3- and 6-month study visit*
Self-reported drug and alcohol use	90-day TLFB	Patient	Baseline 3- and 6-month study visits
Drug or alcohol use severity	CIDI-SAM	Patient	Baseline 3- and 6-month study visits
Problems related to drug or alcohol use	SIP, SIP-D	Patient	Baseline 3- and 6-month study visits
Psychological well-being	GAD-7, PHQ-8	Patient	Baseline 3- and 6-month study visits
Biologic measure of any drug use	Hair testing	Lab result	6-month study visit*
Acceptability to patients of screening and interventions	In-depth interviews	Patient	Individual interviews with 6 patients in each study period

* Hair testing will become not applicable for any patient participant that completes 6 month interview over the phone

PCP assessments in Phase 2, SO and SUSIT conditions:
PCP focus groups: All participating PCPs will be invited to participate in focus groups, which occur prior to the SO period, and again 3 months following implementation of the SUSIT. Focus groups will be conducted by the PI to assess the provider-level factors that are anticipated to have the greatest impact on adoption. In the focus group conducted during the SUSIT period, themes will be explored in the context of their experience with the SUSIT.

Substance abuse attitudes survey: Provider attitudes can influence delivery of SBI to patients.[47,48] Because PCPs may be reluctant to share negative attitudes toward substance use and users in a focus group, we will use the validated Substance Abuse Attitudes Survey (SAAS) to measure subjective norms.[49] Because PCP attitudes may change in response to increased experience addressing substance use in their patients, the SAAS and modified TAM2 questionnaire will also be given at the end of the SUSIT period.

3.2. Data analysis and data monitoring

3.2.a.Data analysis
Qualitative data analysis (Phases 1 and 2):

In-depth interviews and focus groups (conducted in Phases 1 and 2) will be audio taped and transcribed, then coded using Atlas.ti.[50] We will use an a priori coding scheme based on themes related to the TAM2 model elements, and additionally identify any concepts relevant to adoption of the SUSIT that were not included in the a priori list (i.e. emergent themes) using a grounded theory approach. Analysis will be conducted by a 3-person team of Dr. McNeely, Dr. Shelley, and the Research Coordinator (RC). Initial coding of the transcripts will be done by the RC using a coding guide jointly developed by the analysis team. The coding schemes will be continually compared for consistency. The investigators will independently read and analyze the transcribed sessions, then discuss the findings until a consensus is reached on the core categories and main findings.

Audio recordings of medical encounters (conducted in Phase 2, SUSIT condition) will be reviewed and coded by the Research Coordinator using the validated Brief Intervention Adherence Scale (BAS).[51] The BAS is a 21-item checklist developed for the purpose of assessing the content of brief intervention delivered by health care providers, and has been used as a fidelity measure in alcohol SBI trials.[52, 53]

Quantitative data analysis (Phase 2):

The data structure follows a hierarchy of patient-level data nested within providers, during the SO vs. SUSIT study period. For analysis of the primary outcome, which is measured at the patient level, we will first examine whether any brief intervention occurred, in at least one visit, during the study period. For additional descriptive information we will count the number of visits in which an intervention occurred, and the number of elements of the brief negotiated interview documented in each visit. The "receipt of brief intervention" outcome analyses will use a generalized linear mixed model (i.e., multilevel logistic regression)[54-57] with a random intercept and patients nested within primary care providers. The key explanatory variable will be treatment condition (SUSIT vs. SO). When the fixed effect of treatment condition is exponentiated, this coefficient indicates how the odds of receiving brief intervention are multiplied when an individual receives the SUSIT condition rather than screening only. Patient-level and PCP-level covariates (e.g., substances used, provider SAAS score) can be added to the multilevel logistic regression analysis if they are significantly related to the odds of intervention. Any patient-level covariates will be grand mean centered following our focus on treatment condition effects.[58]

3.2.b.Data monitoring

The PI will be responsible for reporting to the IRB and for monitoring all aspects of the study including adherence to the study protocol, quality assurance and adverse events. Monitoring of data quality will be conducted on an ongoing basis by the research team. Data on study enrollment and measures will be reviewed by the PI every 3 months.

While no study-related adverse events (AEs) are anticipated, any study-related adverse event that may occur will be recorded with the name of the event, the relationship to study participation, the severity and resolution. These reports will be reviewed by the PIs within 24 hours and reported to the IRB within 3 days of the adverse event's occurrence. These written reports will be stored in each subject's case file. The PI will review all study-related AEs reported during the previous month for the determination of seriousness, severity and relatedness, and will classify each AE as serious or non-serious. Study-related serious adverse events (SAEs) and unanticipated problems involving risks to participants or others (UAPs) related to study procedures will be reported to the IRB following NYU SoM reporting requirements. New information that may affect study participation will be provided to participants in a timely fashion. Study-related AEs and SAEs will be followed through resolution, stabilization or study end, and any serious and study-related AEs will be followed until resolution or stabilization, even beyond the end of the study. Subjects may be withdrawn from the study if continued participation would be harmful or for non-compliance with study procedures or for a serious adverse reaction to study procedures. The study may be discontinued on the recommendation of the PI or the NYU SoM IRB.

Data Safety and Monitoring Board (DSMB). A safety monitoring board will be established for ongoing protocol review, including data, protocol compliance, safety and efficacy data, in compliance with NIH and NYU guidelines. The DSMB is comprised of John Rotrosen, MD (Chair), Joshua Lee, MD, MSc, and Ryan McCormack, MD, MS.. All board members will meet NIH requirements regarding background and experience, and none will have ethical conflicts, including financial interest related to study outcome. Individuals invited to serve on the board will disclose any potential conflicts in writing. The board will meet every six months (unless more frequent meetings are deemed necessary). At each meeting, Dr. McNeely and other research personnel will report on the trial status. This will be followed by a closed session under the direction of the DSMB chairperson, during which time the investigators and research team may be present. This will be followed by an executive session restricted to DSMB members. Issues discussed may include those related to subject safety and benefit, whether the primary study question is being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues). Following each DSMB meeting, recommendations will be made by the chairperson to Dr. McNeely, and a final report (edited by all DSMB members) will be prepared and submitted to NIDA and the NYUMC IRB. Stopping the study due to safety concerns or interim analysis of the primary outcome are not anticipated.

3.3. Data storage and confidentiality

Data from the screening tool will be securely transferred to a database that resides on a HIPAA compliant cloud-based server; no data is stored on the tablet itself. The data will be backed up daily onto a password-protected secure storage drive. All computerized data (including substance use screening data, interviews, transcripts, audio recordings, screen recordings) is stored in a secure, double password-protected, storage drive that is maintained on a remote server by the NYU School of Medicine, and accessible only to members of the research team. Access to research offices at NYU is restricted to research staff, and the buildings where these offices are located are secure and monitored by security staff. File drawers containing participant information are located only at the NYU research office. These files are kept locked when not in use, and only research staff members have keys to these file cabinets. When the researchers are collecting data at the clinical sites, they will hand-carry a minimum amount of participant information required for that day's study visits on site, in a locked cabinet. At the end of each recruitment day, this information will be hand carried back to the research office and stored in a locked cabinet. Personal health information required to carry out the study (name, contact information, medical record number) will be stored separately from any study assessments. The only link between identifying information and the study ID will be kept in an electronic database, stored on a secure server under a separate password from that required to access the other study information.

Digital audio recordings and screen recordings will be uploaded within 24 hours in which the recording was made, to a password-protected secure storage drive on NYULMC Box. The recordings will be accessible only to members of the research team. Audio recordings will be sent for transcription within one week following the focus group or interview session, and only written transcripts will be used for analysis. Digital audio files will be deleted when data collection and transcription are completed, and video screen recordings will be deleted as soon as the usability testing analysis is completed.

4. Risk/benefit assessment

4.1. Importance of the knowledge to be gained

Substance use accounts for more morbidity, mortality, and disability than any other preventable condition,[1, 2] yet only a small fraction of individuals with unhealthy substance use are served by the specialty treatment system. The technology-assisted approach to screening and intervention that we

propose to study aims to reduce barriers to addressing substance use in primary care patients. This innovative model for a primary care-integrated approach to unhealthy substance use has the potential to improve population health related to drug and alcohol use.

4.2. Risks

This study poses no more than minimal risk to participants. The main risk of participation is loss of confidentiality, which will be guarded against by the measures detailed below. As an additional protection, we will apply for a NIH/NIDA for a Certificate of Confidentiality. Personal identifying information collected for the study will be kept to the minimum required to collect the specified study measures.

Primary care providers: Providers are employees of the study sites Adequate protections will be implemented to ensure that participation in the research does not jeopardize their employment or professional standing. No information about personal substance use will be solicited. Rather, the information gathered will address practice patterns and professional opinions. Provider participants at enrollment only sites will have the same protections as those at the main study sites (Bellevue and Gouverneur Health).

Patients: There is a possibility that participants may feel uncomfortable while completing some study assessments. We will minimize discomfort by having interviews conducted by a trained and qualified research assistant, and in a private space. Participants will be informed that all aspects of their participation are voluntary and that they may choose not to complete assessments or to discontinue their participation entirely, without repercussion or penalty.

In Phase 2, samples are collected from patient participants for hair testing at the 6-month study visit. This will detect common drugs of abuse, as a means of corroborating self-report of recent drug use. Results of hair testing will not be shared with the patient or medical provider. If a participant has to result in having their 6 month interview over the telephone, they will not be required to give a hair sample. This will not have a substantial impact on our findings, as the hair analysis results are only one of many secondary measures (for Aim 3). The primary Aim 3 measure is self-reported drug use, assessed by timeline follow-back interview, which will be done by phone. There are thus two exclusion criteria for the hair sample: (1)having no hair on the head that is at least one-and-one-half inches long; and if the interview is conducted over the phone. RAs will be trained in hair collection procedures through an on-line training provided by the testing company (Omega Laboratories, Inc.). Hair samples will be collected by the RA following the Omega Laboratories collection protocol. Hair samples will be obtained by snipping one-and-one-half inches of head hair using scissors, cut close to the scalp, preferably snipped from the vertex posterior, located at the back of the head, just below the crown. Approximately 60-80 strands of hair are required (in general, the amount needed is the thickness of a shoelace tip). If necessary, hair can be collected from several locations on the head and combined to obtain the required amount of hair. If head hair is not available, body hair may be collected from the axilla(e) or chest. The sample will be identified only by the participant's Study ID, which will be recorded on the Omega Laboratories collection envelope. Samples will be mailed to the Omega laboratory for analysis on the same day they are collected.

4.3. Protections against risks

4.3.a. Informed Consent: Informed consent will be obtained by the researchers from all participants, as per the human subjects research procedures described in Section 5.2. It will be made clear to patients that participation is entirely voluntary. Study staff will err on the side of caution (i.e. lack of eligibility) in deciding if someone is cognitively able to give consent and participate in the study.

4.3.b. Treatment Referral: Individuals who are identified as having high-risk use of alcohol or any

drug during screening, or who self-report pregnancy at baseline, will not be enrolled in the study. They will be linked to the primary care clinic's Social Worker, or that designated clinics' behavioral health care staff, for referral to appropriate substance abuse treatment. Referrals may be made to on-site resources or off-site treatment facilities. The social worker, with assistance from the research team, will facilitate entry to treatment. Bellevue Hospital's addiction treatment services, also serve patients from Gouverneur Health, and are anticipated to be the primary referral site for both of the main study sites. Bellevue offers a wide range of treatment services, including a structured outpatient drug and alcohol treatment program, dual- diagnosis treatment for individuals with co-occurring psychiatric and addiction disorders, and opioid addiction treatment medication (provided through an office-based buprenorphine treatment and a methadone maintenance treatment program). Participants from enrollment only sites, or those from main study sites who prefer to seek treatment outside of Bellevue Hospital, or whose needs may be better met elsewhere, will be offered referral to outside programs by the social worker, or other behavioral health care staff. These patients will additionally receive from the research staff a printed resource list of treatment options, including information on intake procedures. Tobacco screening and cessation assistance are already integrated into usual care at the participating primary care clinics. Bellevue Hospital also has a smoking cessation program, offering group and individual counseling and access to pharmacotherapy, which is available to all clinic patients at the main study sites.

Because all patients being screened for study eligibility are current patients of the primary care clinics or Virology clinic where this study is being conducted, they have the opportunity to seek assistance from their primary care provider or other resources (for example, social worker, nurse, mental health provider, etc.) in the clinic. Participants with PHQ or GAD scores indicating severe depression or anxiety will be advised to speak to their primary care provider and referred by the RA to the psychiatry psychiatry walk-in clinic, or emergency room. Patients who become pregnant during the study will not be withdrawn, but they will be advised by research staff to discuss pregnancy and substance use with their PCP and other clinical staff (OB/GYN, nurse, social worker, etc.). The participating clinics are well equipped to provide patients the behavioral health and other supportive care they need. These resources are provided as part of regular care in the study clinics, and patients will not be restricted from accessing them in any way. Medical and psychiatric emergencies will be handled according to the study's Standard Operating Procedures (SOP).

4.3.c. Privacy and Confidentiality: The personal identifying information collected for the study is kept to a minimum. All consent processes and study assessments will take place in private rooms. Focus groups and interviews will be held in a private room, and will include only participants and members of the research staff. Participants will be informed that audio recordings are made of the focus groups, interviews, and medical visits. For medical visits that are being recorded, the RA will place a digital audio recorder in the exam room and begin recording when the patient and PCP both enter the room. The RA will stop the recording and take possession of the digital recorder as soon as the patient exits the room. The patient and PCP will have the option of stopping or pausing the recording at any time.

Several measures will be taken to insure the confidentiality of the data. Confidentiality will be maintained at all times through the use of unique study numbers on all assessments. We will apply for a Certificate of Confidentiality from NIH/NIDA. Information concerning the Certificate of Confidentiality and its implications will be provided to participants in the consent form(s).

For patients who enroll in Phase 2, the researchers will collect contact information (telephone numbers, address, and email address) to facilitate study retention and scheduling of follow-up study visits. Because in this urban safety net primary care population patients may have unstable housing, participants will also be asked to provide contact information for at least three close

contacts (family, friends) who the researchers could contact by phone or mail if they were unable to locate the participant using their personal information. No personal information will be shared with these close contacts. We will also ask if they work with a social worker or case manager, and if they would allow us to contact them if we were unable to locate participant using their personal information.

For participants in the SUSIT study phase, the research staff will send a clinical reminder to the patient's PCP at each scheduled medical visit that occurs during the study period. Research staff will send these reminders using email or the clinic's secure EHR-integrated message system. It will be sent directly to the PCP only, and will not be accessible to any other than the PCP and the research staff who sent the message. The message sent to the PCP will include the patient's name, medical record number, and substance use screening results from the baseline visit.

At enrollment only sites, the NYU research staff will not access the EHR to view patient information or to communicate with the patient's PCP. The research staff will communicate with PCPs through either secure H+H System email or secure NYU email communications only, and will work with participants and front desk staff to determine the patients' upcoming scheduled appointments.

Transcripts will not contain names or other information that could be used to identify individuals. Participants will be informed in the informed consent sheet that these sessions are recorded for purposes of transcription. Data will be analyzed and reported anonymously.

All study personnel have already taken or will take the mandatory training required by their IRBs, including HIPAA and Patient Privacy/Confidentiality training, to ensure that they are aware of the importance of patient confidentiality and all appropriate laws regarding the protection against patient privacy breaches. Procedures will be in place to ensure that all files containing patient information will be kept in locked filing cabinets and/or password-protected electronic databases. There will also be a system in place for breaches in patient privacy or other adverse events to be reported to the study PI, who will take the appropriate steps to ensure that they are documented and that there is minimal risk that it could happen again.

4.4. Potential benefits to the subjects
There are no direct benefits to patients or primary care providers participating in the study. Participants will receive incentive payments that compensate them for the time spent in study activities. The community at large, including patients and providers, benefits from knowledge gained about substance use, screening and assessment methods, and medical practice that is gathered through this study. The risks to subjects mentioned above are reasonable in relation to these anticipated benefits.

5. Subject identification, recruitment and consent

5.1. Method of subject identification and recruitment
The study protocol and informed consent documents will be reviewed and approved by the Institutional Review Boards of NYU and New York City Health and Hospitals before enrollment begins. Consent will be obtained by trained research staff. Participants will be given a written consent form that includes required language regarding HIPAA and the Certificate of Confidentiality, as well as name and contact information of the PI and of the institutional review board, a description of the study, the payment schedule, a description of potential risks and benefits, a statement of confidentiality, and an indication of the right to refuse or withdraw participation at any time without any consequence. Research staff will review this form verbally and in detail with participants.

Primary care providers: PCPs will be recruited by the researchers via faculty meetings, email, and in-

person.

Patients: Patient participants will be recruited from the adult primary care and virology clinics of Bellevue Hospital or the adult primary care clinic at Gouverneur Health, and from the enrollment only sites. The research team will obtain from the clinic administrator, on a weekly basis, a list of patients scheduled to see participating PCPs for a routine medical appointment. Patients will be approached by a RA in the waiting room, when they present for their medical visit. The RA will inform them of the study, and obtain verbal consent to screen them for study eligibility. Research staff will nt have any information about patients of non-participating PCPs, and no patients of non-participating PCPs will be approached by the RA.

Screening for study eligibility: Patients who agree to screening for eligibility and meet the inclusion criteria for age and language will receive the tablet-based screening tool. The screening tool will be described as a 'computerized questionnaire about health behavior', to avoid biasing participant responses. The RA will present interested patients with an information sheet, and will be present and available for patients who have any questions. Patients will be required to provide verbal consent to proceed. Those who agree to participate will be assigned an anonymous study ID by the screening tool. Those who agree to continue the screening process will self-administer the substance use screening questionnaires on the tablet computer. When substance use screening is complete, research staff will view the patient's substance specific involvement scores (SSIS) on the tablet computer. Patients having moderate-risk use of at least one drug (SSIS 4-26 for any drug), in the absence of any high-risk drug or alcohol use (SSIS 27+ for any drug or alcohol), and meet all other inclusion/exclusion criteria, will be offered participation in the main study. Individuals who do not qualify for the study due to high-risk drug or alcohol use will be informed by research staff of their risk score and its interpretation. They will be offered treatment referrals as detailed in section 4.3.

5.2. Process of consent

Primary Care Providers: For interviews and usability testing activities, a member of the research team will obtain consent in English and/or Spanish via an IRB-approved consent form (described in Section 5.4 below). Participants will provide consent for audio recording of focus groups, interviews, and medical visits. PCPs participating in Phase 1 usability testing will provide consent for both audio and video screen recording, and those participating in Phase 2 will provide consent for audio recording.

Signed consent forms will be filed in a secured cabinet located in the offices of the research team at NYU School of Medicine.

Patients: Patients recruited to Phase 1 will receive paper copies of an information sheet, and will be asked to provide verbal consent for participation. Patients recruited to Phase 2 (SO and SUSIT conditions) will be asked to sign a written consent document. For participants at Bellevue only there will be one copy of the enrolled patient consent form made for the Clinical Research Center at Bellevue, where interviews are conducted. Those consent forms are stored in a double locked unit at the Clinical Research Center (CRC) in Bellevue and only the CRC staff has access to the record room. At all other study sites, including enrollment only sites, interviews will be conducted in a private room that is not located in the CRC, and no copy of the consent form will be made.

Individuals who enroll in a study phase that requires having their screening results delivered to the PCP (i.e. Phase 1 clinical testing phase, or Phase 2 SUSIT condition) will additionally sign a HIPAA authorization for sharing their screening results with the medical provider. Patients who choose to enroll in Phase 2 SUSIT condition will go through a detailed information sheet which will review procedures for sharing the screening results with their provider, the RAs will obtain verbal consent to share those results with their PCP. A separate signed authorization for Audio Recording will be collected before patients meet with their provider.

Beginning in January 2019, for Phase 2 patient participants we will obtain consent to allow the research staff to review primary care provider notes that are documented in the patient's medical during the 12 months following study enrollment (inclusive of the date of enrollment). For participants enrolled in the SUSIT phase, the chart review is included in a revised IRB-approved informed consent document (version date 01/09/19). Participants who previously completed informed consent will be re-consented using the revised informed consent document when they come back for any follow-up appointment with their primary care provider, or at their 3 month or 6 month follow-up study visits.
Participants who were previously enrolled (in the SO or SUSIT phase) and have completed all study visits, and who are not able to meet with research staff in person to complete the revised informed consent document, we will obtain verbal consent over the telephone. In the telephone consent process, research staff will provide information verbally about the study using an IRB-approved script, and will offer to send participants a written information sheet (via regular mail and/or email, depending on the participant's preference). Participants will be given an opportunity to ask questions, and then will be asked to give verbal consent for the chart review. If we cannot reach a study participant over the telephone or in person, we will not conduct the chart review for that individual.

For PCPs and patients, the RA will meet individually with the potential participant, after they have finished with their PCP, in a private area of the clinic and give them a copy of the consent document. The RA will review the contents of the consent document, which contains a description of the purpose of the study and the participant's rights of confidentiality, and review the remaining study activities (which are the baseline and follow-up research assessments). The RA will offer to answer any questions. Following this discussion, and prior to any collection of any study-related information, consent to participate in the study will be obtained. The written consent may be obtained either before or after the visit with the primary care provider, depending on the amount of time that is available (i.e. if patients are called to see their provider before the full consent process has been completed, or if the patient is more comfortable doing this after the visit, the signed consent may be obtained after the patient finishes their visit with the provider).

The 12 patient participants who are recruited to take part in an individual in-depth interview will be purposively recruited from the already-enrolled sample of study participants to achieve a distribution of gender, race, and age. These individuals will receive a written information sheet prior to the interview, and will be asked to provide verbal informed consent for the interview and for audio recording.

5.3. Subject capacity
Prior to enrollment, subjects will be asked to describe the activities required for study participation. Those who are unable to describe these study activities without guidance from the researchers will not be permitted to enroll. Study staff will err on the side of caution (i.e. lack of eligibility) in deciding if someone is cognitively able to give consent and participate in the study.

5.4. Consent forms and Documentation of Consent
All consent documents will include the name and contact information of the PI and of the institutional review board, a description of the study, the payment schedule, a description of potential risks and benefits, a statement of confidentiality, and an indication of the right to refuse or withdraw at any time without any consequence. A separate consent form will be obtained for audio recording of individual interviews, focus groups, or medical visits, and for audio/video recording of usability testing sessions. PCP consent documents will inform them that a decision not to participate will have no bearing on the individual's employability, reputation, professional relationships, or relationship with NYU, New York City Health and Hospitals, or any affiliated individuals.

Patients who enroll in a study phase that requires having their screening results delivered to the

PCP (i.e. the Phase 1 clinical testing phase, or Phase 2 SUSIT condition) will additionally sign a HIPAA authorization for sharing their screening results with the medical provider. The authorization forms will not contain the participant's Study ID or any other links to their study data.

Signed consent documents will be hand carried by the RA back to the research offices at NYU, at the end of each recruitment day. They will be stored in a locked cabinet that is accessible only to study personnel. The consent documents will be stored separately from all other personal health information or assessments that are collected for the study. When a verbal consent is obtained, subjects will be offered the option of having their name recorded as a study participant, but this is entirely voluntary.

The following consent documents will be used in carrying out this study:
Phase 1 consent documents:

1. Phase One PCP interview for CDS development: Information sheet
2. Phase One PCP usability testing: Information sheet
3. Phase One PCP clinical testing: Information sheet
4. Phase One Patient screening: Information sheet
5. HIPAA authorization for patients
6. Audio/video recording consent for PCPs

Phase 2 consent documents:

1. Phase Two Patient screening: Information sheet, paper and electronic
2. Phase Two Patient SO phase participation: Written consent
3. Phase Two Patient SUSIT phase participation: Written consent
   [Note that the SO and SUSIT patient consents are the same, except that the SUSIT consent includes delivery of substance use screening information to the medical provider and consent to audio recording (Section 4-5).]
4. Phase Two PCP participation: Written consent
5. Phase Two Patient interview: Information sheet
6. HIPAA authorization (for patients in the SUSIT condition)
7. Audio recording consent (for PCPs and for patients in the SUSIT condition)
8. Phase Two Chart Review Information Sheet (for participants who provide consent for chart review by telephone)

5.5. Costs to the subject
There are no costs to the subjects associated with this study.

5.6. Payment for participation. Incentives will be provided to participants in the form of cash or a gift card, in the amounts specified below. For interviews conducted over the phone, if they are unable to come to site for incentive, a gift card will be mailed to participant.

Phase 1:

- PCPs who participate in usability testing will receive a $50 incentive.
- PCPs who participate in interviews for CDS content development and clinical testing will take part in a 30-60 minute semi-structured interview with the PI will receive a $50 incentive.
- Patients who participate in CDS clinical testing will complete the tablet-based screening tool, and receive a $5 incentive.

Phase 2:

- PCPs who participate in a 45-minute focus group will receive a $50 incentive.
- PCPs who participate in the SAAS survey (administered twice) will receive a $25 incentive for each survey completed.

- Patients enrolled in the SO or SUSIT condition will receive an incentive for their participation. Incentives escalate in amount with each study visit, to assist with study retention. The baseline visit amount is $20, the month-3 visit is $25 and the month-6 visit (which includes hair testing) is $30. Incentives are not provided for follow-up medical visits.
- Patients who participate in individual in-depth interviews (45 minutes) will receive an incentive in the amount of $50.
- Patients who contact us with a change in primary contact (phone number or email address) will receive $5. They can receive this payment at their next scheduled follow-up appointment, or they can be picked up at clinic site from RA at a scheduled time.

6. Research Team

PI Jennifer McNeely, MD, MS is a NIH-funded researcher who developed the computerized screening tools that will be used in the study. She successfully conducted a large study at the Bellevue Adult Primary Care Clinic (which is the proposed site for the current study) to evaluate the validity, reliability, and feasibility of these tools.

Co-Investigator Donna Shelley, MD, MPH is a senior investigator and a leader in tobacco cessation research whose work has focused on implementation of guideline-recommended tobacco screening and treatment in health care settings. Her work has included developing and testing a tablet-based tobacco clinical decision support device similar to the SUSIT, and using qualitative methods to examine the impact of a CDS system on hypertension management in federally qualified health centers. As Vice Chair for Research in the Dept. of Population Health, Dr. Shelley supports the development of junior investigators, and she and Dr. McNeely have a history of collaboration on research related to SBIRT interventions in dental clinics.

Study personnel will have research training including training in protection of human subjects, and will be directly supervised by the PI. All study personnel have already taken or will take the mandatory HIPAA and Patient Privacy/Confidentiality training modules for the NYU School of Medicine to ensure that they are aware of the importance of patient confidentiality and all appropriate laws regarding the protection against patient privacy breaches.

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