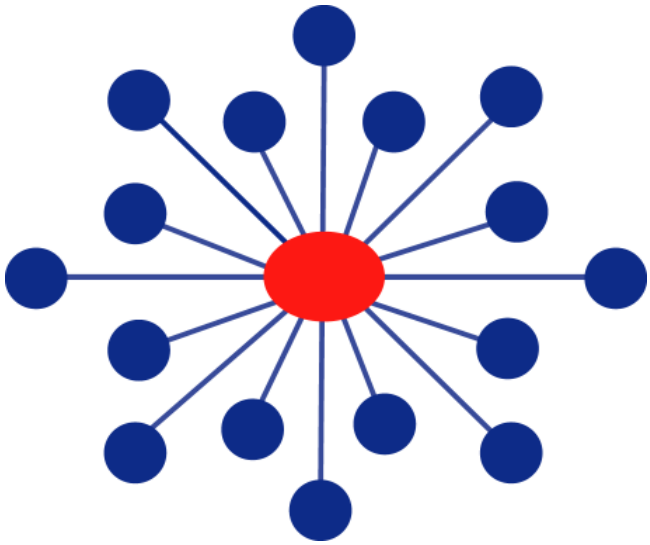

NIDA CTN Protocol 0059

The TAPS Tool: Screen and Brief Assessment Tool Validation Study

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1.0 LIST OF ABBREVIATIONS

ACASI	Audio computer-assisted self-interviewing
API	Application planning interface
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AUC	Area Under the Curve
AUDIT-C	Alcohol Use Disorders Identification Test, Consumption Items
CIDI-SAM-2	Composite International Diagnostic Interview – Substance Abuse Module-2
DSM-5	Diagnostic and Statistical Manual-5
EHR	Electronic Health Record
GCP	Good Clinical Practice
IRT	Item Response Theory
LI	Lead Investigator
RA	Research Assistant
SBIRT	Screening, Brief Intervention, Referral to Treatment
SUD	Substance Use Disorder
TAPS	Tobacco, Alcohol, Prescription medication and other Substances
USPSTF	US Preventive Services Task Force

2.0 STUDY SYNOPSIS AND SCHEMA

2.1 Study Objectives

This study seeks to develop and validate a 4-item screen and a two-stage screening and brief assessment tool to screen and assess primary care patients for tobacco, alcohol, prescription drug, and illicit substance use and problems related to their use. The screen and two-stage screening and brief assessment tool (the latter hereafter called the Tobacco, Alcohol, Prescription medications, and other Substance [TAPS] tool) will be evaluated via self-administration and via interviewer-administration.

Aim 1: To develop a screen and a two-stage brief assessment tool (the TAPS Tool) to detect substance use, sub-threshold substance use disorder (i.e., at-risk, harmful, or hazardous use), and substance use disorders of tobacco, alcohol, prescription medications, and illicit substances among primary care patients.

Aim 2: To examine the validity of both the 4-item screen and the TAPS Tool by comparing them to reference standard screening and assessment measures for substance use, sub-threshold substance use disorder, and substance use disorders.

Aim 3: To determine the feasibility and acceptability of the self-administration and interviewer-administration of the screen and TAPS Tool among adult primary care patients.

2.2 Study Design

Study procedures will begin with a pilot testing phase in which 30 adult primary care patients across the three study sites will provide feedback on their comprehension of the items, and the feasibility, acceptability, and preference for format of the 4-item screen and the TAPS Tool delivered using an iPad during self-administration and interviewer-administration. Following the pilot phase, 2,000 adult primary care participants will be randomly assigned in counter-balanced order to have the interviewer-administration of the screen and TAPS Tool first or the self-administration of the screen and TAPS Tool first (each participant will have the screen and tool administered both ways). Following administration of the screen and TAPS Tool, participants will be surveyed on their views of feasibility, acceptability and preference for format of self-administration versus interviewer-administration of the screen and TAPS Tool. After the survey is completed, the interviewer will administer criterion measures of use, sub-threshold substance use disorder, and substance use disorder.

2.3 Study Population

This study will include a total of 2,000 adults recruited during their primary care visit in the study sites in three CTN Nodes (Mid-Atlantic, New York, and Southern Consortium Nodes). Only those recruited participants who complete the study will be counted toward to the total number of participants required for the study. Participants will be recruited by research assistants in the waiting room. An IRB-approved information sheet will be used to obtain verbal informed consent. Pending IRB approval of the protocol, written consent will not be obtained because the participant's name and signature would constitute the only recorded identifying information of the participant.

2.4 Eligibility Criteria

Inclusion Criteria:

1. Primary care patients ages 18 years or older
2. Ability to provide informed consent

Exclusion Criteria:

1. Inability to comprehend spoken English.
2. Inability to self-administer the iPad tool due to physical limitations.
3. Previously enrolled in this study.

2.5 Assessment

1. The TAPS Tool will consist of a 4-item screen for tobacco use, alcohol use, prescription medication misuse, and illicit substance use in the past year and a brief assessment (modified version of the ASSIST-Lite (Ali et al., 2013)).
2. Participants will complete a brief survey on their view of the screen and tool's feasibility, acceptability, and their preference for format of administration of the screen and tool (self-administration vs. interviewer-administration).
3. Validation assessments include interviewer administered: (a) full ASSIST, (b) 30-day Timeline Follow Back (TLFB) for alcohol, prescription drug misuse, and illicit substance use, (c) modified Composite International Diagnostic Interview – Substance Abuse Module Version 2 (CIDI-SAM V2) for alcohol and all prescription drug and illicit substance use disorder diagnoses, (d) Fagerström Test for Nicotine Dependence (FTND), (e) the smokeless tobacco questionnaire, and, (f) AUDIT-C, (g) oral fluid testing for amphetamines, methamphetamine (including ecstasy/MDMA), cocaine/metabolite, opiates, oxycodone, phencyclidine, THC, barbiturates, benzodiazepines, and methadone.

2.6 Safety Assessment

This is a minimal risk study (survey and oral fluid collection only) that does not include a behavioral or pharmacological intervention. It is unlikely that there will be any adverse event reported. The adverse event forms will be available to report any event that occurs during the single visit.

The only known risk to participants would be loss of confidentiality, although the likelihood of this occurring is quite low given that data will be collected anonymously and the participant's name will not be recorded on a consent form. Any loss of confidentiality will be reported on a protocol deviation form.

2.7 Primary Aim

The goal of this study is to (1) examine a 4-item screen useful for routine identification of tobacco, alcohol, prescription drug misuse and illicit substance use during the past year among adults in the primary care setting and (2) develop a combined 2-stage screening and brief assessment tool (TAPS Tool) for detection of adult primary care patients with problems related to use of tobacco alcohol, prescription medications, or illicit substances. The TAPS Tool might have clinical utility in the primary care setting by not only identifying substance use but also potentially establishing the patient's level of risk (low, medium, high) which could be used to inform their need for brief intervention versus treatment for a substance use disorder. The 4-item screen and the TAPS Tool will be examined to validate a) screen alone and b) the combined screen and brief assessment tool (TAPS Tool).

To achieve this goal, we will collect reference standard measures of tobacco, alcohol, prescription medication, and illicit substance use, including substance use risk level, as assessed by the full ASSIST, substance use disorder status as assessed by the modified CIDI-SAM-2 for all substance use disorders (tobacco, alcohol, individual drug classes), number of days in the past month of alcohol and substance use on the TLFB, Fagerström scores of nicotine dependence, unhealthy alcohol as measured by the AUDIT-C, and recent substance use as measured by oral fluid testing.

2.8 Data Analyses

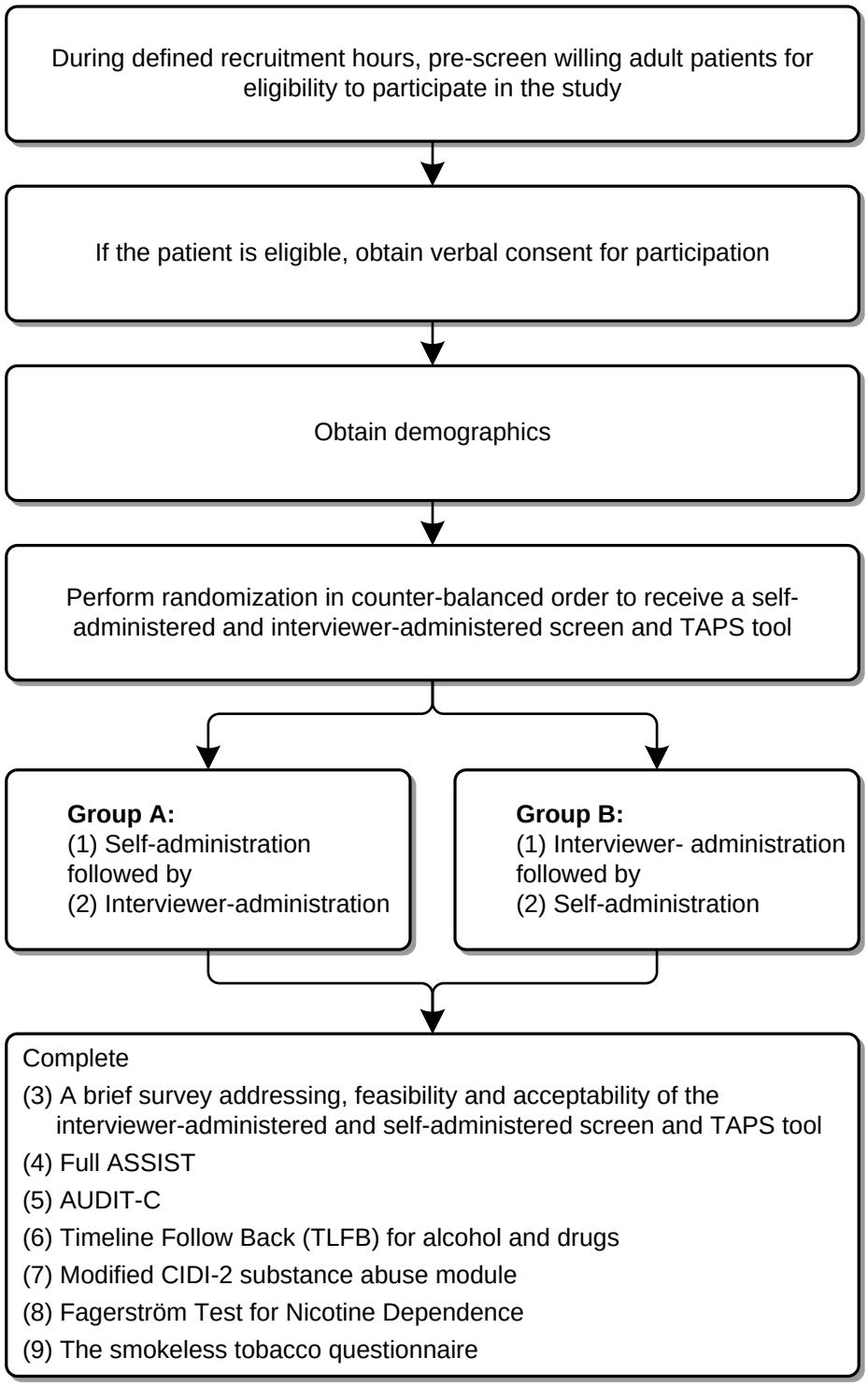
We will conduct separate analyses to examine the validity of the screen alone and of the TAPS Tool. Statistical analyses will examine agreement between different measures of substance use, sub-threshold substance use disorder, and substance use disorder (sensitivity, specificity, area under a receiver operating characteristic curve [AUC]) to evaluate the level of classification accuracy for each item or candidate combination of items. Additional detailed specifications of study variables and analytical procedures are described in the CTN0059 Statistical Analysis Plan (SAP).

2.9 Regulatory Issues

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

3.0 STUDY FLOW CHART OR TIME AND EVENT TABLE

Study Flowchart



4.0 INTRODUCTION

4.1 Background

Substance use disorder (SUD) is under-detected and under-treated in primary care settings. The need for a clinically useful brief screening and assessment instrument to identify patients with substance use, sub-threshold SUD, or a SUD to facilitate brief interventions and referrals to appropriate treatment cannot be overstated (Tai et al., 2012). The Affordable Care Act, the Mental Health Parity Act and Addiction Equity Act, and the Health Information Technology for Economic and Clinical Health (HITECH) Act all provide support and opportunities for integrating evidence-based interventions for SUD in primary care settings. The push for meaningful use of an electronic health record (EHR) system in routine healthcare necessitates developing effective Screening, Brief Intervention, and Referral to Treatment (SBIRT) models (Tai et al., 2012).

However, the field is still lacking a valid combined screen for identifying tobacco, alcohol, prescription drug misuse and illicit substance use in primary care as well as a screening and brief assessment tool for distinguishing between risk levels of the use of these substances, as well as their, sub-threshold use disorder, and SUD in order to guide clinical decision making (Lanier & Ko, 2008; Pilowsky & Wu, 2012; Pilowsky & Wu, 2013; Ghitza et al., 2013; Wu et al., 2012; Wu et al., 2013). In two recently published CTN studies, analyses from factor analysis, item response theory (IRT), sensitivity, and specificity procedures showed that for alcohol and drugs, two items (inability to cut down, taking larger amounts than intended) had a high probability of correctly identifying treatment-seeking patients with a current SUD (Wu et al., 2012; Wu et al., 2013). However, those studies were conducted among populations of patients with substance use disorders in substance abuse specialty care treatment settings. *Tools are needed for use in primary care settings where the patients may be asymptomatic and the prevalence of substance use disorders is lower than substance abuse treatment programs (Lanier & Ko, 2008; Ghitza et al., 2013).*

Previously, Smith et al. (2009) have validated a single-question screener for identifying unhealthy alcohol use among adults in primary care ("*How many times in the past year have you had X or more drinks in a day?*", where X is 5 for men and 4 for women, and a response of >1 is considered positive.). The single-question screen was found to be 81.8% sensitive (95% confidence interval (CI) 72.5% to 88.5%) and 79.3% specific (95% CI 73.1% to 84.4%) for the detection of unhealthy alcohol use. It was slightly more sensitive (87.9%, 95% CI 72.7% to 95.2%) but was less specific (66.8%, 95% CI 60.8% to 72.3%) for the detection of a current alcohol use disorder. Smith et al. (2010) also reported promising results of a single-question screener for identifying drug use among adults in primary care ("How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" A response of at least 1 time was considered positive for drug use.) The reference standard was the presence or absence of past-year drug use or a drug use disorder (abuse or dependence) as determined by a standardized diagnostic interview. Drug use status also was determined by oral fluid testing for common drugs of abuse. The single screening question was found to be 100% sensitive (95% CI, 90.6%-100%) and 73.5% specific (95% CI, 67.7%-78.6%) for the detection of a drug use disorder, and highly sensitive for the detection of self-reported current drug use (92.9%; 95% CI, 86.1%-96.5%) and somewhat less sensitive for drug use detected by oral fluid testing or self-report (81.8%; 95%CI, 72.5%-88.5%). These data demonstrate the utility of developing brief screeners for identifying problematic substance use among primary care patients.

The findings from Smith et al. (2009, 2010) suggest the feasibility of developing a screen clinically useful for identifying not just alcohol use or drug use but also tobacco use. Participants were recruited from a single site, an urban safety-net hospital located in a community where the prevalence of substance use problems is high (Smith et al., 2010). Participants were asked the questions through face-to-face interviewer-administration.

Additional research is required to validate substance use screening items in a more diverse sample of adults in primary care (e.g., multiple sites) and in a computer-based, self-administered version (e.g., on an iPad) is warranted. The use of a screen of multiple substances (tobacco, alcohol, prescription medications, and illicit drugs) in primary care is desired because it reflects patients' drug use patterns and needs for intervention and should effectively facilitate the implementation of screening and brief intervention programs for commonly encountered substances of use or abuse in primary care. Therefore, one of the aims of the proposed study is to examine a 4-question screen for multiple substances (tobacco, alcohol, prescription medications, and illicit drugs) in a diverse sample of adult primary care patients who will be recruited from multiple sites. To meet the need for electronic adoption by an EHR system, the screen as well as the combined screening and brief assessment tool will be evaluated for administration via two-platforms: self-administration and interviewer-administration of the iPad-delivered tool.

Furthermore, many patients in primary care settings can be anticipated to screen positive for substance use, and will require assessment for substance use problems. In the Smith et al. study (2010), for example, 35% of participants reported past year drug use. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST 3.0) is a validated structured interview for assessment of alcohol, tobacco, prescription drug, and illicit drug use and their associated problems in general medical settings (Humeniuk 2008, Mdege and Lang 2011, Humeniuk, Ali et al. 2012, McNeely J. 2013). While ASSIST 3.0 is a comprehensive assessment tool, its length and administration time deter routine use in primary care (Ali et al., 2013). Nonetheless, the ASSIST has some clear advantages over very brief screening tools. Ali and colleagues (2013) derived a shorter version named the ASSIST-Lite (using IRT and other statistical procedures) in a secondary analysis of the multisite ASSIST data; psychometric and classification data indicated empirical support for further testing its use in general medical settings (Ali et al., 2013). In that analysis, for each substance an item pair was selected based on classification values (e.g., area under the receiver-operating characteristic [AUC] curve [0.8–1.0], sensitivity [0.8–1.0], specificity [0.7–0.8]). While promising, the newly developed ASSIST-Lite needs to be modified and tested in primary care settings in the US; evaluated for potential patient self-administration; and delivered using an electronic tablet (such as an iPad) by self-administration or interviewer administration (where results could be integrated into an EHR system to facilitate clinical intervention).

Taken together, this project will address the need to develop a screen (for routine or early identification of recent (past year) tobacco, alcohol, prescription drug, and illicit drug misuse) and a combined screening and brief assessment tool (for detection of different risk levels of substance use to inform optimal clinical management) among adults in primary care settings. To increase the likelihood of widespread adoption of the screen tool by the research community and to facilitate cross-study comparisons, we will test the 4-question screen for the past-year status of substance use problems using language for timeframe (i.e., past 12 months) adopted by the NIH PhenX Toolkit (www.phenx.org) for the DSM-based substance related disorders.

4.1.1 Significance to the Field

The proposed screen and TAPS Tool build on prior work and contain the following essential features to facilitate wider adoption of screening and brief assessment in primary care (Ghitza et al., 2013; Lanier & Ko, 2008; Pilowsky & Wu, 2012; Pilowsky & Wu, 2013; Smith et al. 2009; Smith et al. 2010; Wu et al., 2012; Wu et al., 2013):

- Be brief;
- Be valid;
- Be comprehensive (query several commonly used substances including tobacco, alcohol, misuse of prescription medications, and illicit drugs);
- Use an electronic platform for delivery to facilitate links to EHRs;
- Be valid for either patient self-administration or interviewer administration, to provide the needed flexibility to seamlessly fit into the office workflow;
- Create clinical risk categories based on responses (that are actionable and will subsequently lead to development of interventions to match each level, i.e., clinical decision support); and
- Be available in the public domain for wide dissemination [application planning interface (API), actual tool, etc.].

4.2 Study Rationale

Substance use and its associated problems are among the nation's top public health concern. Substance abuse can affect almost every major organ and result in significant morbidity and premature mortality (Brick, 2008; Clark et al., 2008; Wickizer, 2013). In 2012, 8.5% of the US population aged 12 or older, or an estimated 22.2 million Americans, were estimated to have an alcohol or drug use disorder in a year (SAMHSA, 2013). However, only an estimated 4.0 million Americans aged 12 or older (1.5% of the US population) received treatment for problems related to the use of alcohol or illicit drugs in a year (SAMHSA, 2013). Specifically, the national survey data estimated that just 2.5 million persons, or 1.0% of persons ages 12 or older and 10.8% of persons who needed treatment for alcohol or drug use problems, received behavioral health treatment at a specialty facility in 2012 (SAMHSA, 2013). These numbers demonstrate a major gap in service use for substance use related problems.

The majority of individuals make one or more medical visits in a given year (Pleis et al., 2010); therefore, primary care settings provide a natural location and opportunity for clinicians to screen for substance use and related problems, provide timely interventions, and make referrals to appropriate specialty care. The U.S. Preventive Services Task Force (USPSTF, 2009 and USPSTF, 2013) has recommended primary care delivered screening and brief intervention (SBI) for tobacco use and unhealthy alcohol use among adults. However, in the case of illicit drugs, the USPSTF has determined that there is insufficient research evidence to support such a recommendation (USPSTF, 2008). Yet non-medical use of prescription medications and illegal substance use are prevalent in the general population, and are expected to be even more common in primary care settings due to medical complications of drug use. In 2012, an estimated 23.9 million Americans ages 12 or older currently used illicit substances and/or prescription medications non-medically (SAMHSA, 2013). This estimate represents 9.2% of the general US population ages 12 or older. Marijuana, prescription opioids, and cocaine are among the most commonly misused drugs (SAMHSA, 2013).

During the past decades, various sources of data, including admissions to drug abuse treatment facilities and emergency departments as well as substance-involved mortality statistics, have shown that misuse or abuse of prescription opioids constitutes a major and national public health concern in the US (Straus et al., 2013).

In addition to prescription opioid misuse problems, rates of illicit marijuana use and marijuana use-related treatment admissions have increased (SAMHSA, 2012; SAMHSA, 2013). In particular, major changes in state policy regarding marijuana medical use and legalization have increased the availability of marijuana. There are concerns about the potential impact of these policy changes on increases in marijuana use, unhealthy use, and use disorders as well as marijuana-related mental health symptoms including psychosis (Ruiz-Veguilla et al., 2013; Svrakic et al., 2012). The prevalence of non-medical prescription drug use and illicit drug use supports the need for research to develop an effective screen and a combined screening and brief assessment tool (TAPS Tool) that can be incorporated into routine healthcare in primary care settings to facilitate early detection of, and intervention for, sub-threshold SUD, and SUD. To take into account the diverse needs of different primary care settings (e.g., workflow, caseload, and patient populations), it is also important to validate both an interviewer-administered and self-administered version of the screen and TAPS Tool, as well as to validate the and the TAPS Tool separately so that health systems will have the option of using either a screen or a combined screen and brief assessment tool to, as dictated by the needs of their patient populations and clinical settings.

5.0 OBJECTIVES

5.1 Primary Objective

The primary objective is to develop a 4-item screen and the TAPS Tool (combining 4-item screen with a brief assessment) to be used among primary care patients, and to examine their validities by comparison to reference standard screening and assessment measures for substance use, sub-threshold substance use disorder, and substance use disorders.

5.2 Secondary Objectives

The secondary objectives are to determine the feasibility (time required to complete the screen and TAPS Tool, need for assistance) and acceptability (liking of the tool) for the self-administered and interviewer-administered versions of the screen and the TAPS Tool, among primary care patients.

6.0 STUDY DESIGN

6.1 Overview of Study Design

STUDY GROUP:

Eligible participants will be randomly assigned into one of the two groups: GROUP A and GROUP B. Both groups will first complete a demographic questionnaire (age, gender, race, ethnicity, years of education, current employment status, marital status).

GROUP A:

Will first complete a self-administered TAPS Tool on an iPad and then the same tool via a face-to-face interview (also administered on an iPad). Following tool administration, the RA will survey the participant regarding feasibility and acceptability of the interviewer-administered and self-administered versions of the tool. This will include the RA's observations regarding the amount of time it took to complete each format as well as the participant's need for assistance during the tool administration.

GROUP B:

Will first complete face-to-face interviewer-administration and then self-administration of the tool. Following tool administration, the RA will administer the survey and record observations as described above for Group A.

The RA will administer to both Groups the following reference standard assessments for substance use, sub-threshold SUD, and SUD:

- Full ASSIST for all substances.
- AUDIT-C.
- Timeline Follow Back (TLFB) interview.
- Modified CIDI-SAM 2 for all substance use diagnoses (tobacco, alcohol, and drugs).
- Fagerström Test for Nicotine Dependence (FTND).
- Smokeless tobacco questionnaire.
- Oral fluid testing for amphetamines, methamphetamine (including ecstasy/MDMA), cocaine/metabolite, opiates, oxycodone, phencyclidine, THC, barbiturates, benzodiazepines, and methadone. Oral fluid testing will be accompanied by a review of current medications to determine whether any of the drugs included in the oral fluid test are being prescribed. RAs will have medication picture cards from the National Survey on Drug Use and Health as a reference in case a participant is unable to recall the name of a medication.

Blinding:

Participants will not be blinded to study group. The interviewer will be blinded to the sequence of self-administration vs. interviewer-administration until after the patient provides informed consent.

Study Components:

Study components will include:

- An individualized pilot test of 30 adult primary care patients (across the study sites) to obtain feedback on the user-friendliness of the initial versions of the tool.

- Data collection from 2,000 adults using both formats for administration of the tool (2000 completers); reference standard assessments for substance use, sub-threshold SUD, and SUD.

- A short survey of participants' views of acceptability of the self-administered and interviewer-administered versions of the tool.

6.2 Duration of Study and Visit Schedule

Following the pilot test, the study plans to recruit over a period of 10 months a total of 2,000 adults (ages 18 or older), who complete the study from all sites combined. Each participant will be seen only once for this study (no follow-up visits). Initial screening and all assessments will occur during the participant index visit. The total duration of individual participation in the study is expected to be from about 30 minutes to 1 hour (depending on how many substances they report having used).

Compensation:

To increase participants' retention to complete all assessments and to compensate participants for their time, each participant will be paid $20 for completing the assessments and an additional $10 for providing an oral fluid sample for drug testing.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

1. Primary care patients ages 18 years or older at one of the participating CTN Node study sites.

2. Ability to provide informed consent.

7.2 Exclusion Criteria

1. Inability to comprehend spoken English.

2. Inability to self-administer the iPad tool due to physical limitations.

3. Previously enrolled in this study.

7.3 Subject Recruitment

For a target sample size of 2,000 adult completers, the New York Node site is expected to recruit approximately 40 participants per month (approximately 10 adults per week per site) in order to reach the recruitment target (400 completers) within 10 months. The site/s in Mid-Atlantic Node and Southern Consortium Node will be expected to recruit approximately 80 participants per month (approximately 20 per week) in order to reach the recruitment target (800 completers) within 10 months. However, the sites may continue to recruit competitively after they have reached their recruitment target until the entire study reaches 2,000 participants who have completed all of the assessments.

It is assumed that 50% of primary care adult patients who are approached to explore their willingness to participate in the study either decline or are ineligible for the study. The participants will be directly recruited from the clinic's waiting rooms, after obtaining IRB approval.

7.3.1 Special Populations to Consider

Given the demographic characteristics of the study sites, we will be able to recruit an adequate sample of women and nonwhite participants. Participants who are considered prisoners by OHRP guidelines will not be included in the study.

7.4 Study Sites

7.4.1 Number of CTN Node Study Sites

There will be three CTN Nodes with several study sites involved in the study:

- Mid-Atlantic Node.
- New York Node.
- Southern Consortium Node.

7.4.2 Study Site Characteristics

Study site characteristics were developed based on the need to obtain data from adult patients enrolled in primary care. Sites will be selected from among clinics with the following characteristics:

1. Primary care clinic.

2. Clinic serves a sufficient number of male and female patients that would be potentially eligible to participate in the study.

3. Clinic has adequate space to accommodate study staff and activities.

7.4.3 Rationale for Study Site Selection

The selection of study sites is based on the applicability of the expected finding to adults in the community, cost, and feasibility. For consideration of the generalizability of study results to community-based primary care patients, the study will be conducted in primary care settings.

8.0 OUTCOME MEASURES

8.1 Primary Measure of Interest (Screen, TAPS Tool)

Unlike an intervention trial that seeks to examine a specific outcome in relation to an intervention, the focus of this study is to identify a set of questions useful for detecting adults with use, sub-threshold SUD, and SUD of tobacco, alcohol, prescription medications, and illicit drugs. Thus, we plan to examine the sensitivity, specificity, and ROC for each item of a) the 4-item screen and b) the TAPS Tool, against items from this study's gold standard measures. As such, all items of the screen and TAPS will be examined.

8.2 Criterion Measures

The Full ASSIST, AUDIT-C, TLFB, modified CIDI-SAM-2, Fagerström, smokeless tobacco questionnaire, and Oral Fluid Testing will be the gold standards (criterion) in separate analyses for each corresponding substance (tobacco, alcohol, cannabis, etc.) as appropriate. We intend to examine each item in the TAPS Tool, against the corresponding item(s) on the gold standard measures. Thus, for example, the tobacco item on the TAPS Tool would be compared to the tobacco item on the ASSIST, while the marijuana item on the TAPS Tool would be compared to the marijuana item on the ASSIST. Furthermore, we want to compare the TAPS Tool scores by substance with the "gold standard measure" (Full ASSIST for all substances, Fagerström for tobacco, and modified CIDI-SAM-2 for all substances) to determine whether they met criteria for a sub-threshold SUD or SUD for that particular substance use disorder.

9.0 STUDY PROCEDURES FOR PILOT TESTING OF SCREEN AND TAPS TOOL

After the programming and testing of the electronic version of the TAPS Tool is completed (including a measurement of administration time for both the screening and brief assessment sections separately and in total), the investigators will conduct a pilot test with 30 participants across the study sites. Adult primary care patients will be recruited and asked to complete the interviewer-administered and self-administered (iPad) versions of the TAPS Tool and subsequently asked during an individual meeting with study staff to provide their feedback on the tool.

During the use of the iPad, the research assistant will observe the participant's use of the iPad, ask about any visible difficulty, and make text notes describing problems and remediation to address this difficulty.

After the participants complete the tool, they will be asked to complete a brief survey asking about the feasibility (e.g., time required to complete [in minutes]; user-friendliness [Likert scale 1 to 5]; need for assistance: [yes/no with comment box]), acceptability (e.g., comprehension of the items including smokeless tobacco item [yes/no with comments box], likelihood of responding accurately [Likert scale]), and preference for format (self-administration versus interviewer-administration [preference choice vs. no preference]) of the tool in primary care settings.

These survey items will be rated by participants on a 5-point Likert Scale to capture their view of their experience with the interview-administration vs. self-administration of the tool. The survey will be as follows:

How much do you agree with the following statements on a scale of 1-5 where:

1 = strongly disagree **2** = disagree **3** = neither agree nor disagree **4** = agree **5** = strongly agree

Q1. These questions were easy to understand.

Q2. I was comfortable answering these questions.

Q3. I answered these questions as honestly as I could.

Q4. I would be willing to answer questions like these at my doctor's office.

Q5. I think my friends would answer these questions honestly at their doctor's office.

Q6. The iPad touch screen was easy to use.

Q7. I would prefer that a person asked me these questions in the doctor's office instead of answering them myself on the iPad.

Q8. I would prefer answering these questions on an iPad instead of having a person ask me.

Q9. The voice recording was helpful.

Q10. I would be comfortable sharing my answers about drug use with my doctor.

Each participant will be paid $20 for their time and contribution to the study. Based on each participants' response, the screen and TAPS Tool will be refined to improve the wording and workflow accordingly.

10.0 STUDY PROCEDURES FOR PRIMARY STUDY OF THE TWO-STAGE TOOL

10.1 Recruitment and Informed Consent Procedures

Study recruitment procedures:

To avoid interrupting patient care, the logistics of conducting screening in a medical setting require that the screening process be relatively brief. During defined recruitment hours, research staff assigned to the study will screen primary care patients who are possibly eligible for the study. Depending on the patient flow, patients will be approached either prior to or after the evaluation by a clinician.

Research staff will approach patients consecutively in the clinic waiting area and ask them if they are willing to participate in anonymous screening for participation in a health study. Participants will provide verbal (not signed) consent for the anonymous collection of screening data, using a brief IRB-approved script. For each day of screening, the number of patient refusals and other reasons for patient inability to participate will be recorded on the Recruitment Form to determine whether they met inclusion criteria (and if not, why not: lack of spoken English comprehension; younger than 18 years old; unable to provide informed consent, physically unable to use the iPad, or other). The RA will document the screening and eligibility status of all individuals approached on the Recruitment Form. The research staff will screen patients according to the Operations Manual procedures and local manual of operations. Screening efforts will continue until recruitment hours have ended.

Informed consent procedures:

Informed consent will be obtained in a two-step process. In the first step, eligible patients who agree to participate in the study will be provided with an IRB-approved informed consent information sheet. The IRB will be asked to waive written informed consent because it is a minimal risk study, and the consent form would be the only place in which the name of the participant would be recorded. The information sheet will include a description of all significant elements of the study: the assessment interview and questionnaires; risks and benefits of study procedures; alternatives to participation in the study; confidentiality; $20 payment for participation; a statement that participation is voluntary and that the patient may withdraw at any time; and information about whom to contact with questions. The consent form will also indicate that the decision to participate will in no way influence other aspects of the patient's treatment. Patients will read the first paragraph of informed consent information sheet (or have it read to them, if they are unable) and express verbally their understanding of the key elements of the study (e.g., random assignment, the approximate duration of assessments, and risks of participation).

After completing the assessments, participants will be asked to provide informed consent (using an IRB-approved consent form with waiver of written consent) to participate in the second step of the study in which they would provide an oral fluid sample for testing amphetamines, methamphetamine (including ecstasy/MDMA), cocaine/metabolite, opiates, oxycodone, phencyclidine, THC, barbiturates, benzodiazepines, and methadone. They would be told that drug testing data will be collected without a link to their name or other identifiers and that they are free to refuse to provide the sample. They will be informed they would receive an additional $10 for providing the sample. Participants will not be asked to provide consent for the oral fluid

test until after they have completed all other study assessments in order to avoid biasing the self-reported data.

10.2 Randomization

After providing the initial informed consent, participants will be randomly assigned to one of the two groups according to a block randomization procedure within site.

The research staff will use an Enrollment Form to document inclusion and exclusion criteria and any reasons for which an eligible participant is not randomized.

GROUP A will complete a self-administration of the two-stage instrument and then a face-to-face interviewer-administration of the same instrument.

GROUP B will complete face-to-face interviewer-administration of the two-stage instrument and then a self-administration of the instrument.

10.3 Blinding

The CTN Data and Statistics Center (DSC) statistician will generate the randomization scheme for the study. The randomization procedure will be conducted through a centralized, web-based process set up by the CTN DSC. The randomization sequence will be unknown to staff until after the participant provides informed consent.

10.4 Participant Compensation

Adequate compensation for time and inconvenience for this study is appropriate and will consist of $20 to each participant who completes the pilot test (*N*=30). Participants in the main study (*N*=2,000) will receive $20 for completing the survey instruments and an additional $10 for providing the oral fluid specimen.

10.5 Subject Discontinuation

All participants are allowed to withdraw consent at any stage of the study. In addition, the research assistant or PI can remove the participant from the study when there is evidence that continuing in the study might be harmful to the participant.

11.0 STUDY TIMETABLE

The study will recruit for approximately 10 months after launch, and lock the database eight weeks after the final visit.

12.0 STUDY ASSESSMENTS

The selection of assessments is based on consideration for the reported validity of the selected assessments, need for comprehensive data to select a useful set of screening and assessment items for developing a screen and the TAPS Tool, as well as costs of data collection in terms of participant time, staff time and training, and feasibility of completion in a general medical setting. Therefore, assessment questions are limited to those that have demonstrated clinical value and can contribute directly to the objectives of this study.

Each participant will respond to 4 screening items followed by the TAPS Tool which is based on the modified ASSIST-LITE.

The four screening items were based on previous reports (NIH, 2011; Smith et al., 2009; Smith et al., 2010) and modified for the present study by asking about “how often” rather than on “how many days” did the participant use substances. The five response options for the screening questions may create risk categories and are consistent with NIDA CTN's extensive work on common data elements. They are based on the response categories used in the ASSIST, but modified for easier comprehension by replacing the option “once or twice” with “less than monthly”.

Each participant will complete two formats for the screen and TAPS Tool: self-administration on an iPad, and an interviewer-administration with responses entered by the RA on the iPad. The sequence of the assessment format will be randomly assigned (See Section 8.2). This will be followed by a brief survey regarding comprehension, feasibility and acceptability of the computer-administered and the interviewer-administered tool. Finally, the RA will administer the reference standard assessments.

12.1 Protocol Specific Activities/Assessments

Protocol Specific Assessments				
CRF	**Done by**	**Screening for eligibility**	**A two-stage tool**	**Additional measures**
Recruitment Form	RA	X		
Informed consent	RA	X		
Enrollment/Randomization*	RA			
Demographics	RA			X
4-item screen for tobacco, alcohol, medications, illicit drugs	RA, Participant		X	
TAPS Tool	RA, Participant		X	
Survey on comprehension, feasibility, acceptability, and preference for format	RA			X
Timeline Follow Back	RA			X
ASSIST-Full	RA			X

Protocol Specific Assessments				
CRF	**Done by**	**Screening for eligibility**	**A two-stage tool**	**Additional measures**
AUDIT-C	RA			X
Modified-CIDI-SAM-2	RA			X
Fagerström Test for Nicotine Dependence (FTND)	RA			X
The smokeless tobacco questionnaire	RA			X
Recent Prescription Medication Use	RA			X
Oral fluid testing	RA			X
Protocol Deviation Log	RA			X
Compensation Log	RA			X
Study Termination	RA			X

* Participants will be randomly assigned in counter-balanced order to receive a self-administered two-stage instrument and a face-to-face interviewer-administered two-stage instrument.

12.1.1 Laboratory Tests

Following the interview, participants will be asked to provide an additional verbal informed consent (see above) to undergo oral fluid testing for the presence of common drugs of abuse (amphetamines, methamphetamine (including ecstasy/MDMA), cocaine/metabolite, opiates, oxycodone, phencyclidine, THC, barbiturates, benzodiazepines, and methadone). Once collected, oral fluid will be sent to an outside laboratory for analysis using methods that yield results comparable to urine drug screening (Intercept® immunoassay; OraSure Technologies, Bethlehem, Pennsylvania)). To aid in the interpretation of drug test results, individuals will be asked, as part of the testing procedures, if they are currently taking any drugs as prescribed by their health care provider(s) from a list of prescription opioids, benzodiazepines, and stimulants (and logged by the RA onto a CRF “Recent Prescription Medication Use”). RAs will have medication picture cards from the National Survey on Drug Use and Health as a reference in case a participant is unable to recall the name of a medication.

After completing the interview, participants will be compensated ($20 if they complete the interview only and $30 if they complete both the interview and the oral fluid testing) and thanked for their participation. Individuals who meet criteria for SUD of alcohol or drugs (e.g., other than tobacco) will be offered local substance use treatment referral resources, while those with current tobacco use will be given the number for their state quitline.

12.1.2 Clinical Assessments

Stage I – Substance use screening questions
Proposed 4 – Item Screen:

The screen will consist of one stem question with 4 substance categories.

(Instructions: The following questions are about the past 12 months)

Question - In the past 12 months, how often have you:

1. Used any tobacco (for example, cigarettes, e-cigarettes, cigars, pipes, or smokeless tobacco)?
2. [Males] Had 5 or more drinks containing alcohol in one day?

   [Females] Had 4 or more drinks containing alcohol in one day?

   [Only the version specific to participant's gender will be administered].

   - 1 standard drink is about 1 small glass of wine (5 oz), 1 beer (12 oz), or 1 single shot of liquor
3. Used any drugs including marijuana, cocaine or crack, heroin, methamphetamine (crystal meth), hallucinogens, ecstasy/MDMA?
4. Used any prescription medications just for the feeling, more than prescribed,, or that were not prescribed for you?

   Prescription medications that may be used in this way include:

   - Opiate pain relievers (for example, OxyContin, Vicodin, Percocet, methadone).
   - Medications for anxiety or sleeping (for example, Xanax, Ativan, Klonopin).
   - Medications for ADHD (for example Adderall or Ritalin).

Response Options (regarding the past 12 months):

- Daily or almost daily
- Weekly
- Monthly
- Less than monthly
- Never

Stage II - Brief assessment questions
TAPS Tool (modified ASSIST-Lite)

(Instructions: The following questions are about the PAST 3 MONTHS ONLY)

1)	**Did you smoke a cigarette containing tobacco?**	Yes [1] No [0]	→ *No: Skip to Q2*
1a	Did you usually smoke more than 10 cigarettes each day?	Yes [1] No [0]	
1b	Did you usually smoke within 30 minutes after waking?	Yes [1] No [0]	*Tobacco score: __ [0-3]*
			Cut-off = 2
2)	**Did you have a drink containing alcohol?**	Yes [1] No [0]	→ *No: Skip to Q3*
2a	On any occasion, did you have 5 or more drinks containing alcohol in a day (for men)/ 4 or more drinks containing alcohol in a day (for women)? *	Yes [1] No [0]	
2b	Have you tried and failed to control, cut down or stop drinking?	Yes [1] No [0]	*Alcohol score:* __ [0-4]
2c	Has anyone expressed concern about your drinking?	Yes [1] No [0]	
* 1 Standard drink is about 1 small glass of wine (5 oz), or 1 beer (12 oz), or 1 single shot of liquor			*Cut-off = 3*
3)	**Did you use marijuana (hash, weed)?**	Yes [1] No [0]	→ *No: Skip to Q4*
3a	Have you had a strong desire or urge to use marijuana at least once a week or more often?	Yes [1] No [0]	
3b	Has anyone expressed concern about your use of marijuana?	Yes [1] No [0]	Cannabis score: __ [0-3]
			Cut-off = 2
4)	**Did you use cocaine, crack, or methamphetamine (crystal meth)?**	Yes [1] No [0]	→ *No: Skip to Q5*
4a	Did you use cocaine, crack, or methamphetamine (crystal meth) at least once a week or more often?	Yes [1] No [0]	
4b	Has anyone expressed concern about your use of cocaine, crack, or methamphetamine (crystal meth)?	Yes [1] No [0]	Stimulant score: __ [0-3]
			Cut-off = 2
5)	**Did you use heroin?**	Yes [1] No [0]	→ *No: Skip to Q6*
5a	Have you tried and failed to control, cut down or stop using heroin?	Yes [1] No [0]	
5b	Has anyone expressed concern about your use of heroin?	Yes [1] No [0]	Heroin score: __ [0-3]
			Cut-off = 2

These next questions are about taking prescription medications just for the feeling, more than prescribed, or that were not prescribed for you. Please do NOT report use of 'over the counter' medications.

Stage II - Brief assessment questions
TAPS Tool (modified ASSIST-Lite)

(Instructions: The following questions are about the PAST 3 MONTHS ONLY)

6)	**Did you use a prescription opiate pain reliever (for example, Percocet, Vicodin) not as prescribed or that was not prescribed for you?**	Yes [1] No [0]	→ No: Skip to Q7
6a	Have you tried and failed to control, cut down or stop using an opiate pain reliever?	Yes [1] No [0]	
6b	Has anyone expressed concern about your use of an opiate pain reliever?	Yes [1] No [0]	Opioid score: __ [0-3] Cut-off = 2
7)	**Did you use a medication for anxiety or sleep (for example, Xanax, Ativan, or Klonopin) not as prescribed or that was not prescribed for you?**	Yes [1] No [0]	→ *No: Skip to Q8*
7a	Have you had a strong desire or urge to use medications for anxiety or sleep at least once a week or more often?	Yes [1] No [0]	
7b	Has anyone expressed concern about your use of medication for anxiety or sleep?	Yes [1] No [0]	*Sedative score:* __ [0-3] Cut-off = 2
8)	**Did you use a medication for ADHD (for example, Adderall, Ritalin) not as prescribed or that was not prescribed for you?**	Yes [1] No [0]	→ *No: Skip to Q9*
8a	Did you use a medication for ADHD (for example, Adderall or Ritalin) at least once a week or more often?	Yes [1] No [0]	
8b	Has anyone expressed concern about your use of a medication for ADHD (for example, Adderall or Ritalin)?	Yes [1] No [0]	Stimulant score: __ [0-3] Cut-off = 2
9)	**Did you use any other illegal or recreational drug (for example, ecstasy/molly, GHB, poppers, LSD, mushrooms, special K, bath salts, synthetic marijuana ('spice'), whip-its, etc.)?**		Not scored –

What did you take? _____

Stage III – A brief survey of views on use of the screen and TAPS Tool:

As participants complete the self-administered and interviewer-administered screen and TAPS Tool, the RA will record, for each mode of administration, any interruptions during administration of the screen or tool [in minutes], the number of times the participant requests assistance, and the type of assistance requested (reading, comprehension, use of the iPad, or other recorded in comments box).

After the participants complete the screen and TAPS Tool, they will be asked to complete a brief survey asking about the feasibility (e.g., user-friendliness; need for assistance), acceptability (e.g., comprehension, likelihood of responding accurately, user friendliness), and preference for format (self-administration and interviewer-administration) of the tool in primary care settings.

The following survey items will be rated by participants on a 5-point Likert Scale to capture their view of their experience with the interviewer—administered and self-administered versions of the tool.

How much do you agree with the following statements on a scale of 1-5 where:
1 = strongly disagree
2 = disagree
3 = neither agree nor disagree
4 = agree
5 = strongly agree
Q1. These questions were easy to understand.
Q2. I was comfortable answering these questions.
Q3. I answered these questions as honestly as I could.
Q4. I would be willing to answer questions like these at my doctor's office.
Q5. I think my friends would answer these questions honestly at their doctor's office.
Q6. The iPad touch screen was easy to use.
Q7. I would prefer that a person asked me these questions in the doctor's office instead of answering them myself on an iPad.
Q8. I would prefer answering these questions on an iPad instead of having a person ask me.
Q9. The voice recording was helpful.
Q10. I would be comfortable sharing my answers about drug use with my doctor.

Stage IV - Comparison instruments for validation purposes, all of which are administered by the RA in a face-to-face interview

1. **Full ASSIST:** The ASSIST provides substance-specific information and provides scores for each substance. The instrument has been shown to be a valid measure of substance use involvement, with good feasibility, reliability, and validity (Newcombe et al., 2005; WHO ASSIST Working Group, 2002). The ASSIST probes several non-medical use dimensions during the past 3 months and lifetime for specific substances, including tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, sedatives, and opioids. It generates substance specific involvement scores with validated cutoffs corresponding to low-risk, moderate-risk, or high-risk use. Each 'past 3 month' item on the ASSIST is rated on a 5-point interval scale of never, once or twice, monthly, weekly, and daily or almost daily, with different corresponding scores for each value depending on the question. Lifetime questions have response categories of either: 'yes' or 'no'; or 'no', 'yes but not in the last 3 months', and 'yes, within the last 3 months'.
2. **AUDIT-C:** The World Health Organization's Alcohol Use Disorders Identification Test consumption items (AUDIT-C) is a widely used and validated measure of unhealthy alcohol use among medical patients. It is a 3-item questionnaire about consumption of alcohol that can be administered by an interviewer or self-administered (we will use only the interviewer administered version). The AUDIT-C will be used as a comparison measure because it is the most widely used and recommended current screening approach in primary care settings, and it collects information that is distinct from that gathered using the CIDI-SAM. (Reinert and Allen 2002, Bradley, DeBenedetti et al. 2007).
3. **Timeline Follow-Back:** Timeline Follow-Back will be used to assess the use of alcohol, cannabis, heroin, prescription opioids, prescription stimulants, cocaine or crack, methamphetamines, prescription sedatives/hypnotics, and other drugs (e.g., inhalants, hallucinogens) in the past 30 days. This technique, widely used in drug abuse research, consists of a careful review by the RA with the research participant of their substance use over in this case a 30 day time period preceding the interview (Sobell & Sobell, 1992). The RA will use a calendar and review key events (such as birthdays, holidays) to anchor the dates in the month.
4. **Modified CIDI-SAM-2:** The CIDI-SAM-2 will be used to assess tobacco, alcohol and all drug use diagnoses. The CIDI-SAM-2 is a comprehensive instrument used to assess substance use disorders to ICD-10 and DSM-IV criteria (Forman et al., 2004). Substance abuse disorders covered in the CIDI-SAM-2 are alcohol, tobacco, and nine categories of illicit drugs. Questions mapping to the DSM-IV diagnostic criteria for substance abuse and dependence are asked in a past 12 month time frame. In the current study, the CIDI-SAM-2 will be modified by dropping all the questions that are not used to obtain a DSM-5 substance use disorder diagnosis. In addition, the CIDI-SAM-2 question on craving will be retained so that the DSM-5 criteria for substance use disorder can be obtained. We will use the CIDI-SAM-2 as the "gold standard" for identifying DSM-5 substance use disorders (i.e., patients who should be classified as high risk on a screening instrument).
5. **Fagerström Test for Nicotine Dependence (FTND):** (Fagerström et al., 1990; Heatherington et al., 1991). The FTND consists of three yes/no items scored 0 (no) and 1 (yes) and three multiple-choice items scored from 0 to 3.The items are summed to yield a total score of 0-10. Nicotine dependence is classified in the following manner: 0-2 Very low; 3-4 Low; 5 Moderate; 6-7 High; and, 8-10 Very high. The FTND has shown good reliability (Agrawal et al., 2011; Pomerlou et al., 1994), although more research is needed on the diagnostic validity of the FTND (Meneses-Gaya et al., 2009).

6. **Smokeless Tobacco Questionnaire:** (Institute of Medicine, 2007; American Cancer Society Cancer Action Network, 2012). Smokeless tobacco is a problem that has been associated with oral cancer (Harris et al., 2013). For this reason, data will be collected on the past 3 month use of such tobacco products. Did you use any smokeless tobacco product (snus, dissolvable tobacco tablets, chewing tobacco, or any other product containing tobacco) for more than 5 times a day? Did you use any smokeless tobacco product (snus, dissolvable tobacco tablets, chewing tobacco, or any other product containing tobacco) for more than 10 times a day? Did you usually use a smokeless tobacco product within 30 minutes after waking? Did you use e-cigarettes (yes/no). If yes, how many times per day?
7. **Oral fluid samples for biological measures of objective validation:** All participants will be invited to provide an oral fluid sample to test for amphetamines, methamphetamine (MDMA), cocaine/metabolite, opiates, oxycodone, phencyclidine, THC, barbiturates, benzodiazepines, and methadone. Samples can be analyzed by enzyme immunoassay (EIA). Oral fluid testing has been found to have adequate reliability compared to urine testing. (Bosker & Huestis, 2009; Cone & Huestis, 2007).

12.1.3 Safety Assessments

This study will not involve the use of any clinical intervention or medications. Any adverse event that does occur will be reported on an adverse event form. The only expected risk to participants is a loss of confidentiality which will be minimalized by not obtaining signed informed consent and through anonymous data collection. Any breach of confidentiality will be reported on a protocol deviation form.

12.2 Training Procedures

All research staff will receive GCP training, protocol specific training, database training, and protocol specific assessment training applicable their specific roles and responsibilities before the study initiation. EMMES (NIDA DSC) will provide web-based training sessions for research staff at each site.

In addition, all research staff will complete site-specific training on human subjects research protection and receive certificates of completion.

13.0 STATISTICAL ANALYSIS

13.1 General Design

This study seeks to develop a 4-item screen (tobacco, alcohol, prescription medications, and other drugs) and a two-stage screening and brief assessment tool (called the TAPS Tool) that consists of the same 4-item screener followed by a brief assessment (using the modified ASSIST-lite). The screen and TAPS Tool will be evaluated for self-administration on an iPad and an interviewer-administered delivery.

Study procedures will include (a) pilot testing of the screen and TAPS Tool by 30 adult primary care patients to obtain feedback on their comprehension of the items and on the user-friendliness of the iPad version of the tool. Following review of the pilot data and possible modification of the screen and tool, participants will be administered the screen and tool via the two formats of administration (assigned at random) followed by a survey of comprehension, feasibility, acceptability, and preference for format of administration. Then, the RA will administer reference standard assessments.

13.1.1 Study Hypothesis

This study will not test any intervention or hypothesis. It will focus on the level of agreement between participants' responses to different sets of screening and assessment questions. Items that are considered to measure similar domains of substance use behaviors are expected to have a high level of agreement. The goal of the project is to develop and test a brief screen and the TAPS Tool. As such, the study is a measurement development project and so has no primary outcome variables.

It is expected that there will be no difference between positive responses on substance use between the self-administered screen or the TAPS Tool (delivered on an iPad) and the interviewer-administered screen and TAPS Tool.

It is expected that positive responses from the screen alone and on the TAPS Tool will show a high degree of agreement with well-validated screening and assessment measures.

13.1.2 Primary and Secondary Outcomes

The focus of this study is to identify a set of questions useful for detecting adults with use, sub-threshold substance use disorder, and substance use disorder of tobacco, alcohol, prescription medications, and illicit drugs. As such, in a study of this nature, there are no primary or secondary outcome variables.

13.2 Rationale for Sample Size

To meet the goal of this study, the targeted sample size is expected to provide good precision of sensitivity and specificity of the screen and TAPS Tool when comparing to measures that are considered the gold standard (i.e., ASSIST and/or CIDI-SAM 2). To determine the most appropriate sample size, we performed simulations to calculate the precision of the estimates (specificity and sensitivity) as a function of prevalence and sample size. With a sample size of 2000 completers, we would have good precision of estimates (for sensitivity and specificity) on substances that are of moderate levels of prevalence (i.e., prevalence 5% or greater).

Based on prevalence estimates from a recently completed study in the adult primary care clinic of the New York City site, and known higher rates of prescription opioid misuse in the North Carolina sites, we anticipate having adequate precision to evaluate the tool's accuracy with respect to identifying sub-threshold SUD or SUD for the following substances: tobacco, alcohol, cannabis, cocaine, sedatives, heroin, and prescription opioids. For details regarding the sample size calculation approach see CTN-0059 Statistical Analysis Plan.

13.2.1 Projected Number of Sites and participants

The study will be conducted at primary care settings in three CTN Nodes: Mid-Atlantic Node (n = 800), Southern Consortium Node (n=800), and New York Node (n=400). However, the sites may continue to recruit competitively after they have reached their recruitment target until the entire study reaches 2,000 participants who have completed all of the assessments.

13.3 Statistical Methods for Primary and Secondary Measures

Statistical analyses will examine agreement between different measures of substance use (sensitivity, specificity, area under a receiver operating characteristic curve [AUC]) to evaluate the level of classification accuracy for each item or candidate combination of items. Considerations in determining the statistical approach can be found in the CTN-0059 Statistical Analysis Plan.

13.4 Exploratory Analyses

Exploratory analyses will be conducted to explore whether sensitivity, specificity, AUC differ as a function of factors such as gender, race/ethnicity, and education level. Exploratory analyses will also examine like combinations of substances (e.g., all opioids, all stimulants, illicit drugs other than marijuana, all prescription drugs) as described in the CTN-0059 Statistical Analysis Plan.

13.5 Missing Data and Dropouts

This study does not include follow-up assessments, and all study assessments will be completed during the visit. Missing data and dropouts are expected to be relatively minimal. Nonetheless, the analysis will determine the extent of missing data for all study variables and explore differences in missing data by age, gender, and race/ethnicity. No attempt will be made to impute missing data. The extent of missing data will be evaluated to determine their association with the mode of assessment.

13.6 Demographic Characteristics

See Section **7.3**.

14.0 REGULATORY COMPLIANCE AND SAFETY

14.1 Statement of Compliance

This study will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local institutional review board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports will be submitted to each IRB, according to its usual procedures.

14.2 Regulatory Compliance

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for the regulatory documents compliance prior to study initiation, throughout the study, as well as at the study closure.

14.3 Confidentiality

By signing the protocol signature page the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. Based on communication with the NIDA certificate of confidentiality officer, this study will be conducted without a certificate of confidentiality because data will be collected anonymously and no contact information will be obtained because follow-up interviews will not be conducted.

14.3.1 Health Insurance Portability Accountability Act (HIPAA)

Protected health information will not be collected during the study.

14.3.2 Investigator Assurances

Each community study clinic site must file (or have previously filed) a Federal Wide Assurance (FWA) with the DHHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

14.3.3 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will have an up-to-date signed financial disclosure form on file with their institution and follow other institutional requirements.

14.3.4 Inclusion of Women and Minorities

Women and minorities will be included in the study at all study sites.

14.3.5 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for regulatory compliance prior to study initiation, throughout the study, as well as at the study closure.

14.3.6 Records Retention and Requirements

All records relating to this study will be retained for at least five years after completion of the research and will fulfill their IRB and sponsor record retention requirements. The five-year time period begins when the individual institution's engagement in the human subject research activity ends.

14.3.7 Informed Consent

The informed consent process is a means of providing information regarding the study to a prospective participant and allows for an informed decision about participation in the study. Because this study is minimal risk and data will be collected at only one visit and will be collected anonymously, only verbal consent will be obtained. However, IRB-approved informed consent information sheets will include all of the required elements of informed consent. Each study site must have the study informed consent information sheet approved by their IRB(s). A copy of the IRB-approved consent information sheet, along with the IRB study approval, must be sent to the Clinical Coordinating Center (CCC) and the Lead Node (LN) prior to the site initiation visit. Every study participant will be given a copy of the informed consent information sheet about the study and oral swab specimen collection.

Research staff who are knowledgeable about the study will explain the study to the potential participant and provide the individual with a copy of the consent information sheet to read. If the patient is interested in participating in the study, a research assistant who is authorized to obtain informed consent by the PI and if applicable by the IRB, will review each section of the informed consent information sheet in detail and answer any questions the participant may have. The participant will consent verbally. Persons delegated by the PI to obtain informed consent must be listed on the Site Staff Delegation of Responsibilities and Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate training.

The informed consent information sheet must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect participants' participation in the study. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

14.3.8 Clinical Monitoring

Investigators will host periodic visits by NIDA contract monitors who will ensure all study procedures are conducted and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, both remotely and on site, at mutually agreed upon times, regulatory documents, case report forms (CRFs), and corresponding source documents for each participant.

Qualified node personnel will provide site management for each site during the study. Node staff will verify that study procedures are properly followed and that site staff members are trained and able to conduct the protocol appropriately. If findings indicate that additional training of study personnel is needed node staff will undertake or arrange for that training. Details of data monitoring are found in the study QA monitoring plan.

14.3.9 Study Documentation

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, IRB correspondence and approved consent form.

14.4 Safety Monitoring

14.4.1 Data and Safety Monitoring Plan (DSMP)

This study is not an intervention trial and will not require a Data and Safety Monitoring Board. The Lead Investigator along with the Co-Lead Investigator and sub-investigators are responsible for adhering to the data and safety monitoring plan.

14.4.2 Protocol Deviation Reporting and Management

A protocol deviation is any departure from procedures and requirements outlined in the protocol. Protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system. Additionally, each site is responsible for tracking and reporting to their IRB as required. The CCC and the Data and Statistics Center and the Lead Investigator must be contacted immediately if an unqualified/ ineligible participant is randomized into the study.

14.4.3 Adverse Events (AEs)

This study will not use any intervention and medications. There are no expected adverse events during the sole single study visit in which a series of questionnaires will be administered and an oral swab will be self-administered by the participant to collect a specimen for anonymous drug testing. Any adverse event that does occur during this visit will be recorded on an adverse event form. The name of the event, the relationship to study participation, the severity and resolution will all be recorded. Adverse events will be entered into the data system within 3 days of their occurrence and follow up will not extend beyond the single study visit.

15.0 DATA MANAGEMENT AND PROCEDURES

15.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC). The DSC will be responsible for development of the electronic case report forms (eCRFs), development, and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. A web-based distributed data entry model will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical studies are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

15.2 Site Responsibilities

The data management responsibilities of each individual study site will be specified by the DSC and outlined in the Data Management plan.

15.3 Data Center Responsibilities

The DSC will: 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating sites, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

15.4 Data Acquisition and Entry

Data entry into electronic CRFs (eCRFs) shall be performed by authorized individuals. Selected eCRFs may also require the investigator's written signature or electronic signature, as appropriate. Electronic CRFs will be monitored for completeness, accuracy, and attention to detail throughout the study.

15.5 Data Editing

Completed data will be entered into the DSC automated data acquisition and management system. If incomplete or inaccurate data are found, a data clarification request will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into the DSC automated data acquisition and management system in accordance with the data management plan.

15.6 Data Transfer/Lock

Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

15.7 Data Training

The training plan for study site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of computerized systems, as required.

15.8 Data QA

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

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