

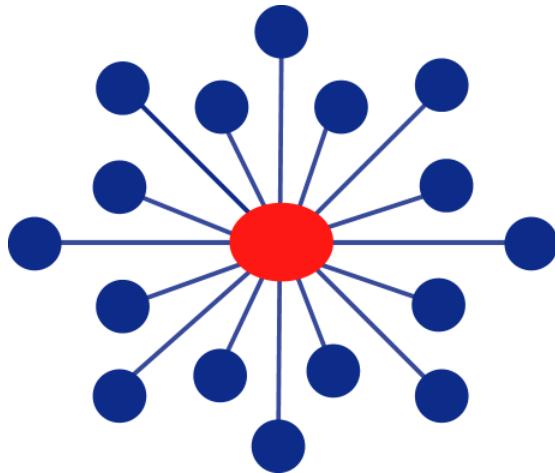
Study Protocol

CTN-0093: Validation of a Community Pharmacy-Based Prescription Drug Monitoring Program

Risk Screening Tool

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VALIDATION OF A COMMUNITY PHARMACY-BASED PRESCRIPTION DRUG MONITORING PROGRAM RISK SCREENING TOOL (PHARMSCREEN)

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Full Name
AUC	Area under the curve
BPI	Brief Pain Inventory
CTN	Clinical Trials Network
LI	Lead Investigator
NS Metric	Narcotic Score Metric
OVN	Ohio Valley Node
OUD	Opioid use disorder
OESW-D	Overdose Experiences, Self and Witnessed-Drug
PHQ-2	Patient Health Questionnaire-2
PDMP	Prescription Drug Monitoring Program
POMI	Prescription Opioid Misuse Index
POUD	Prescription opioid use disorder
ROC	Receiver operating characteristic
SF-12	Short Form-12
TAPS	Tobacco, Alcohol, Prescription medication and other Substances
WHO ASSIST	World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test

2.0 STUDY SYNOPSIS

2.1 Study Objectives

Using opioid therapy to treat pain effectively, while minimizing potential adverse consequences, is an important goal. Appriss Health has developed the “Narcotic Score,” referred to as the “NS metric” hereafter, which uses Prescription Drug Monitoring Program (PDMP) data on opioid and sedative prescriptions and aberrant drug behavior (e.g., multiple providers, pharmacies, etc.) to compute a score quantifying the extent of the patient’s risk for opioid-related adverse events in relation to all prescription opioid users. The association between the NS metric and other indicators of opioid use or risk has not been evaluated, and hence, the degree to which this metric is a useful clinical screening tool is unknown. In addition to the NS metric, the Tobacco, Alcohol, Prescription medication and other Substances (TAPS) tool is rapidly becoming recognized as a high-quality substance use screening measure for outpatient health care settings. Given the somewhat limited opioid-using sample in the TAPS tool validation study ($\leq 5\%$ for prescription opioids; $< 4\%$ for heroin¹), the current study provides the opportunity to (1) to better assess the validity of the TAPS Tool as it would be used in clinical practice in community pharmacy settings (including rural locations), and (2) to provide more clinically useful information for the use of the TAPS Tool by community pharmacists. The present study has two objectives:

- 1) Evaluate the concurrent validity of the NS metric as a clinical measure of high risk opioid use and establish clinically useful risk-level thresholds relative to the widely validated gold standard of the World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST).²
- 2) Collect TAPS tool data in a large sample of individuals filling opioid pain medications to facilitate further validation of this instrument with the WHO ASSIST.

2.2 Study Design

This study is a one group, cross-sectional, health assessment study. Participants who enroll in the study will complete on-line surveys of opioid utilization and risk, overdose history, substance use, mental health, and physical health at a single time point. Appriss Health will provide NS metric scores for all participants. These data will also be used to 1) validate and to identify clinical cut-off values for the NS metric and 2) to further validate the TAPS tool.

2.3 Study Population

Approximately 1,523 patients will be recruited from approximately 15 community Kroger community pharmacies. Trained pharmacy staff will inform potentially eligible participants, or individuals receiving at least one prescription(s) for potentially eligible participants, of the survey opportunity. Interested patients will complete an encrypted electronic “interest survey,” which will trigger REDCap to email the patient a link to a secure web-portal containing e-consent (i.e., an electronic information sheet that is submitted by participants indicating their consent to participate in the study) and self-screening assessment forms. Following submission of the e-consent and successful qualification on the self-screening assessment, the health survey will be made available to participants for completion. The REDCap audio features will be enabled to allow participants with any reading difficult to request specific items be read out loud.

2.4 Assessments

The key assessments are: 1) The NS metric, obtained from Appriss Health, which is a continuous indicator on a 000-999 scale (higher scores indicate increased risk for adverse opioid-related

outcomes);^{3,4} 2) The WHO ASSIST; and (3) the TAPS Tool. The WHO ASSIST and TAPS Tool will be completed by participants through a secure REDCap-hosted web portal. Other assessments to be captured via self-report through the secure REDCap-hosted web portal include: 1) opioid medication misuse assessed with the Prescription Opioid Misuse Index (POMI);⁵ 2) pain severity assessed by the Brief Pain Inventory (BPI);⁶ 3) general health status measured with a 1-item subscale from the Short Form (SF)-12;⁷ 4) depression assessed with the Patient Health Questionnaire (PHQ)-2;⁸ and 5) overdose frequency history assessed using the Overdose Experiences, Self and Witnessed (OESW-D)—Drug instrument.⁹

2.5 Analyses

A series of *a priori* analyses will be conducted to evaluate the validity of the NS metric relative to the widely validated gold standard WHO ASSIST and to identify cutoff thresholds. *A priori* analyses will involve conducting Receiver Operating Curve Analyses (ROC; i.e., sensitivity and specificity, area under the curve [AUC]) to identify clinical cutoff values for the NS metric and low, moderate, and high WHO ASSIST scores. We will also conduct correlational, regression, and Cohen's Kappa statistical analyses to evaluate the relationship between the NS metric and the WHO ASSIST.

We will also conduct *exploratory* correlational and regression, and Cohen's Kappa statistical analyses to validate the relationship between the NS metric and measures of opioid medication misuse as well as history of opioid overdose. Exploratory ROC, correlational, regression, and Cohen's Kappa statistical analyses between the WHO ASSIST and the TAPS Tool will also be conducted.

3.0 STUDY SCHEMA

- Adult patients at participating Kroger Pharmacies in Ohio and Indiana will be approached while picking up qualifying opioid medications
- Pharmacy staff shares details of study
- Persons picking up medications for others will receive a study flyer with instructions on how the opioid recipient may remotely complete the interest form



- Patient inputs contact information into REDCap interest form
- Patient receives email link to e-consent and self-screening assessment



- Upon successfully qualifying on the self-screening assessment and completing the e-consent, the health assessment survey is made available to the participant



- Participant completes survey, which includes:
 1. WHO ASSIST
 2. POMI
 3. TAPS Tool
 4. OESW-D
 5. PHQ-2
 6. SF-12 (general health subscale)
 7. BPI
 8. Demographics



- Ohio Valley Node (OVN) staff verifies the participant has not previously completed the survey and, if verified, sends participant \$50



- Data are checked for completeness, stored in HIPAA compliant environment, and merged regularly with NS metric
- Final merged dataset with NS scores and health assessments are shared with OVN and University of Utah
- Data are analyzed and results are reported

4.0 BACKGROUND AND RATIONALE

4.1 Background

The US opioid epidemic continues to have serious public health ramifications. In 2017, nearly 11.1 million individuals in the US reported misuse of opioid pain-relievers in the past year,¹⁰ with approximately 36% obtaining opioid medications for misuse through filling medications from a prescriber.¹⁰ A robust literature in the last decade has documented a clear trajectory for individuals who begin with opioid medication misuse transitioning to heroin use.¹¹⁻²² In 2017, over 650,000 individuals in the US reported past-year heroin use.¹⁰ Fatal overdose deaths involving prescription opioids, heroin, and synthetic opioids has continued to increase across the US—continuing to increase in 35 states from 2013-2017.²³ Given these persistent trends for adverse opioid-related outcomes in populations across the US, it is critical to work to identify those who are at risk, deliver appropriate care that will help prevent progression to more severe opioid-related outcomes, and provide referral and treatment resources to those who suffer from opioid use disorder (OUD). Therefore, it is necessary to expand the continuum of care to health care settings that previously may have been underutilized.

One underutilized resource for addressing the current opioid epidemic is community pharmacies. In the US, 93% of individuals live within 5 miles²⁴ of the >60,000 community pharmacies that employ >170,000 pharmacists.²⁵ National data show that >40% of community pharmacies have private counseling rooms where pharmacists can discretely and confidentially provide care.²⁶ Pharmacists are ranked among the top 2 most trusted professionals in the US,²⁷ with research showing patients are willing to receive behavioral health information from these professionals.²⁸

Previous research among pharmacists has further provided support for possible identification and intervention by community pharmacists for opioid misuse among patients. Results of a survey in 2 states (N=739) about opioid medication misuse and possible screening and intervening found that most pharmacists (90%) wanted to help patients who misuse opioid pain medications but reported needing training (81%) and tools (80%) to effectively do so.^{29,30} Furthermore, results from 333 patients (response=71.2%) screened in 4 community pharmacies receiving opioid medications found opioid medication misuse among 15% of patients.³¹ Among those with misuse, 98% had ≥ 1 comorbid health condition known to increase risk for misuse or overdose, including depression, posttraumatic stress, risky alcohol use, and poor health and pain exceeding US norms. Patients in this sample were agreeable to pharmacists screening their opioid medication use (70.9%) and discussing medication use if pharmacists had a concern (82.1%; with no differences between misusing and non-misusing respondents, $p>.05$).^{32,33} Given this important foundation for the expansion of the role of community pharmacy to address the opioid epidemic, it is critical to identify opportunities to better equip these health care professionals with tools to identify patients who are at risk for opioid-related adverse events.

The most important clinical tool pharmacists have available to identify possible misuse of opioid medications is prescription drug monitoring programs (PDMP),³⁴⁻⁴¹ which capture patient-level prescription dispensing information to inform monitoring, dispensing decisions, and possible intervention.^{35,36,38,41} These tools are available in all US states (Missouri relies on a county-administered program) and have the potential to enable pharmacists to identify patients at-risk for opioid-related adverse events, such as addiction and overdose. Appriss Health is the largest PDMP platform vendor in the US, providing PDMP services statewide in 42 states, with approximately 1 million users. The Appriss platform facilitates PDMP data sharing in 44 states and captures 8 million monthly transactions. PDMP programs, such as the Appriss platform, have demonstrated clear results for reducing opioid prescribing.³⁵⁻⁴¹ PDMP effectiveness has not been clear on substance use outcomes,³⁸ including rates of overdose.⁴²⁻⁴⁴ PDMP output data are limited

in clinical utility, do not provide decision support, and thus users must act on “best judgment” to provide patient care and referrals with a limited evidence base. Appriss Health has developed an opioid risk measure, the NS metric, which could support community pharmacists’ decision-making regarding interventions for opioid risk. However, the validity of the NS metric has not been evaluated.

4.2 Rationale

In light of the continued escalation of the opioid epidemic nationally, combined with the promising opportunities afforded by the further inclusion of community pharmacy settings for engaging patients with opioid-related risk, it is important to evaluate whether current PDMP risk metrics correlate with clinically validated opioid risk tools and if clinically meaningful risk cutoffs exist for PDMP risk metrics. The present study will accomplish two important objectives.

First, the NS metric has not been empirically validated with standardized opioid risk tools. This formative research project will leverage public/private partnerships among the OVN, University of Cincinnati, University of Utah, Purdue University, Appriss Health, and Kroger Pharmacies to validate and identify risk thresholds for the NS metrics through comparison with the widely validated gold standard WHO ASSIST. Successfully completing this objective is the first important step in understanding the validity of current PDMP metrics and establishing clinically meaningful risk tools for opioids, which would allow community pharmacists to accurately and rapidly triage patient opioid risk. These results will provide foundational data that will allow our team to continue this line of research and further collaborate with Appriss Health to identify and test a PDMP-based, opioid-focused, decision support tool for community pharmacies.

The second objective of this study is to further validate the TAPS tool. Mentioned previously, the TAPS tool is rapidly becoming recognized as a high-quality substance use screening measure for outpatient health care settings.¹ The recent validation study for this tool, conducted with primary care patients, showed high levels of sensitivity and specificity for tobacco and heavy alcohol use (≥ 0.79), and adequate sensitivity and specificity for illicit and prescription drug use (≥ 0.63).¹ Given the somewhat limited opioid using sample in the validation study ($\leq 5\%$ for prescription opioids; $<4\%$ for heroin¹), the current study provides the opportunity (1) to better assess the validity of the TAPS Tool as it would be used in clinical practice in community pharmacy settings (including rural locations), and (2) to provide more clinically useful information for the use of TAPS Tool by community pharmacists.

4.3 Significance to the Field

The first study objective builds on previous research from our team that has focused on understanding the needs and opportunities available for identification of, and intervention for, problematic opioid use among community pharmacy patients prescribed opioid medications.^{29,30,45-47} The results of this project stand to meet several important needs of community pharmacy to increase their involvement in the identification of patients at-risk for opioid-related adverse events, such as addiction and overdose. Specifically, if the first objective is achieved, the results from this study would enable rapid identification of opioid-related risk utilizing data from a widely-available PDMP platform vendor (Appriss Health).

The second study objective also builds on previous research from CTN investigators^{1,48} and stands to extend the knowledge base in the field regarding the utility of the TAPS Tool as a universal substance use screening instrument for outpatient clinical care settings.

5.0 OBJECTIVES

5.1 Primary Objective

The primary objective of this project is to validate and identify low, moderate, and high risk thresholds for the NS metric through comparison to the widely validated gold-standard WHO ASSIST measure for opioid use risk in adult community pharmacy patients dispensed opioid medication therapies.

5.2 Secondary objective

The secondary objective of this study is to collect data to further validate the TAPS Tool. This measure will be compared to the WHO ASSIST in a novel sample of adult outpatients from community pharmacies with active opioid medication prescriptions.

6.0 STUDY DESIGN

6.1 Overview of Study Design

We will implement a one-time, cross-sectional, self-administered, health survey among eligible adult patients dispensed opioid medications from 15 participating Kroger pharmacies in Ohio and Indiana. This design will accomplish the purpose of the study given that it will allow for recruitment of a sample of patients with sufficient power to identify and validate clinical threshold values for the NS Metric. Patients recruited will complete a series of validated measures to assess opioid use and risk behaviors, substance use, and physical and mental health.

Study survey data will be merged on a regular basis with the NS metric by Appriss Health and shared with OVN and University of Utah investigators for assessment of data quality and to conduct statistical analyses. See section 11.9 for an overview of Data Quality Assurance. Appriss Health will deterministically match and merge the survey data with the NS metric using patient contact information (e.g., name, address, phone number) as well as information regarding the location of the pharmacy and time/dates for when the study interest form was completed and submitted into REDCap.

6.2 Duration of Study and Visit Schedule

Enrollment is expected to take place over a period of approximately 6-8 months. Enrolled participants will complete surveys at a single time point, which will take approximately 35-40 minutes to complete.

6.3 Recruitment Sites and Participant Selection

6.3.1 Site Selection

Participating University sites for this project include, the: University of Cincinnati, University of Utah, and Purdue University. Recruitment sites for the study include approximately 12 Kroger Pharmacies in Ohio and approximately 3 rural Kroger Pharmacies in Indiana. The rural Indiana pharmacy locations will be identified as rural by meeting at least one of the definitions of rural using the “Am I Rural” online tool (<https://www.ruralhealthinfo.org/am-i-rural>).

6.3.1.1 Recruitment Site Characteristics

Study site characteristics reflect the need to recruit community pharmacy patients receiving opioid medications in urban and rural settings in order increase the generalizability of the study results. For study feasibility, it was determined that each recruitment site also needed to be a Kroger pharmacy in the state of Ohio or rural Indiana that filled an adequate number of patients’ opioid prescriptions. The Kroger Pharmacy chain was selected as the partner for this project based on 4 primary reasons:

1. Sites selected will dispense an average of ≥ 300 patients’ opioid prescriptions within a 6-month period, resulting in a patient pool of approximately $\geq 4,500$ potential participants;
2. Kroger and Appriss Health have a long history of collaboration, and therefore partnering on this project will be familiar to both companies. Kroger also has a long history of collaboration with University of Cincinnati and Purdue University.
3. Kroger is the 5th largest pharmacy chain in the US, and thus represents a possible scalable service setting if the primary objective of the current study is successful.

4. Kroger corporate offices are located in Cincinnati, Ohio. Thus, working with company leadership and staff training will be facilitated by proximity to the OVN investigative teams at the University of Cincinnati and Purdue University Indianapolis campuses.

In addition to the above points, the study investigative team will work closely with Kroger Pharmacy to select pharmacy locations within ethnically and racially diverse populations to promote the recruitment of a diverse study sample.

6.3.2 Participant Selection

This study will enroll approximately 1,523 patients who will complete a web-based health survey.

6.3.2.1 *Inclusion Criteria*

Potential participants must:

1. be dispensed ≥ 1 opioid medication (including tramadol) by a participating Kroger Pharmacy;
2. be ≥ 18 years of age according to Kroger Pharmacy data and self-report

6.3.2.2 *Exclusion Criteria*

Potential participants must not self-report:

1. solely filling buprenorphine or buprenorphine combination products i.e., patients receiving OUD treatment with no other opioid medication use;
2. currently receiving treatment for cancer;
3. having previously completed the survey (this will be re-verified by OVN staff by examining identifying information following health assessment submission);
4. having current involvement with the criminal justice system that has, or could, lead to incarceration

Mentioned above, we will enable REDCap audio features to allow participants with any reading difficult to request specific items be read out loud.

7.0 STUDY ASSESSMENTS

7.1 Overview of Assessments

The selection of assessments was based on the validity of the assessments, costs of data collection in terms of participant time and staff time and training, and feasibility of completion.

7.2 Primary Measures of Interest

Unlike a clinical trial evaluating the impact of an intervention, the present study is a validation study, and thus, does not include traditional outcome measures.

7.2.1 NS metric

The NS metric is a continuous indicator on a 000-999 scale, with the last digit representing number of active opioid prescriptions (those with ≥ 9 prescriptions coded as 9) and the first two numbers representing a composite risk score. Higher scores indicate increased risk for adverse opioid-related outcomes (e.g., overdose). The first two digits of the score are based on deterministic calculations^{3,4} and use well-known indicators associated with opioid-related adverse events.⁴⁹⁻⁵² These calculations are produced through the following steps:

- 1) For a given patient, raw indicators of five risk factors are extracted from PDMP data: (a) morphine milligram equivalents (MME) dispensed, (b) lorazepam milligram equivalents (LME) dispensed, (c) overlapping prescription days, (d) number of prescribers, and (e) numbers of pharmacies.
- 2) Each raw indicator is converted to a scaled value between 0 and 99 (based on percentiles from a large PDMP reference population), for four time periods: (a) past 2 months, (b) past 6 months, (c) past 12 months, and (d) past 24 months. Therefore, each patient is assigned 20 scaled percentile values. These scaled values weigh the contribution of recent values more heavily than values further in the past; for example, having 6 unique prescribers over the past 2 months has a greater scaled percentile score (i.e., 85) than having 6 unique prescribers over the past 2 years (i.e., 30).
- 3) Scaled values for each of the five indicators are averaged across their four respective time periods.
- 4) A weighted sum of the five averaged values is calculated: MME is given a weight of 3; overlapping medication days is given a weight of 2; and LME, number of prescribers, number of pharmacies are each given a weight of 1. This sum is divided by 8 to produce a weighted average, yielding a two-digit composite risk score; these are the first two digits of the NS metric.
- 5) The total number of active opioid prescriptions is appended to the two-digit composite risk score, to form the final three-digit NS metric.

7.2.2 WHO ASSIST

The WHO ASSIST will be used as the gold standard to which the NS metric will be compared. The WHO ASSIST was constructed in a large-scale multi-country study, which demonstrated criterion, construct, concurrent, discriminant validity.² This assessment contains between 8-74 Likert scale items, depending on the number of substances endorsed by study participants, and will require 5-15 minutes to complete. The WHO ASSIST asks about use of the following

substances in the past 3 months and lifetime: tobacco, alcohol, cannabis, cocaine, amphetamine, inhalants, sedatives, hallucinogens, opioids, and other drugs.

In addition to the WHO ASSIST, we will capture 2 additional opioid items from an adapted WHO ASSIST, developed by McNeely, et al.⁵³ In this adapted version, opioid items specifically inquire about use of prescription opioids and heroin. These items have been tested in an audio assisted computerized format and have demonstrated reliability.⁵³ These items will *not* be used in our a priori assessment of the NS score and the WHO ASSIST.

7.2.3 TAPS Tool

Substance use will also be captured using TAPS 1/2 tool, which has demonstrated concurrent validity.¹ This assessment contains between 5-14 items regarding a respondent's substance use in the last 3 and 12 months. It specifically addresses use of tobacco and alcohol as well as illicit and prescription drug misuse. This assessment will require 5-15 minutes to complete. This measure will be captured to provide additional information regarding its psychometric properties compared to the WHO ASSIST.

7.3 Other Study Measures

Additional measures of opioid misuse, overdose, health, and mental health will also be collected in order to describe the participant population, adjust analytical models, and perform exploratory analyses.

7.3.1 Prescription Opioid Misuse Index

Opioid medication misuse will be captured using the Prescription Opioid Misuse Index, which has demonstrated criterion validity.⁵ This measure contains 6 yes/no items about an individual's current use of opioid medications and covers domains such as early refills, taking more than prescribed, doctor shopping, and using the medication to cope with problems. This assessment will require 5 minutes or less to compete.

7.3.2 Overdose Experiences, Self and Witnessed—Drug

Overdose frequency history will be assessed using the overdose frequency item from the criterion-valid Overdose Experiences, Self and Witnessed—Drug instrument.⁹ This single item asks respondents how many times in their lifetime they have experienced a drug overdose. This assessment will require 1 minute or less to compete.

7.3.3 Brief Pain Inventory

Pain severity will be assessed using the Brief Pain Inventory (BPI), a well-validated, reliable instrument that consists of a 4-item pain Intensity subscale and a 7-item pain interference subscale.⁶ This BPI will require 5 minutes or less to compete.

7.3.4 Short Form-12

General health status will be measured using a 1-item subscale from the construct-valid Short Form-12.⁷ This Likert scale item asks respondents to rate their general health from excellent to poor. This assessment will require 1 minute or less to compete.

7.3.5 Patient Health Questionnaire

Depression will be captured using the criterion-valid Patient Health Questionnaire-2.⁸ This 2-item assessment asks respondents to rate on a Likert scale (ranging from 'not at all' to 'nearly

every day') their interest or pleasure in doing things and feeling of being down or depressed in the last two weeks. This assessment will require 1 minute or less to complete.

7.4 Safety Measures

This study will not involve the use of any clinical intervention or medications. The only expected risk to participants is a loss of confidentiality, which will be minimized by utilizing an encrypted REDCap platform. Any breach of confidentiality will be reported on a protocol deviation form. Data security will also be ensured for transferring data files to and from Appriss Health by utilizing a HIPAA compliant, encrypted, and secure data storage cloud site.

7.5 Other Measures

7.5.1 Recruitment/Screening Assessments

Recruitment – Kroger Pharmacy staff will aid in tracking which patients have been provided with information about the study and how that information was shared.

Interest form – Participants interested in learning more about the study will complete an electronic “interest form” in which they provide their contact information as well as basic demographic characteristics (e.g., age, sex, race/ethnicity). Kroger pharmacy staff will be available to answer participant questions regarding the interest form. If completing the interest form remotely, study staff’s contact information will be available for potential participants to call for assistance.

7.5.2 Self-screening assessment

Following e-consent, participants will complete a self-screening assessment, which will include questions about opioid medication prescriptions (including Kroger Pharmacy at which the qualifying prescription was filled), whether they are being treated for cancer, have involvement with the criminal justice system, and whether they have participated in the study previously. Study staff’s contact information will be shared on the e-consent form, self-screening assessment, and the health survey. They will be available to answer any questions the participant may have.

7.5.3 Additional PDMP Data

Appriss Health may also provide, in addition to the NS metric, other related data that possibly will be informative for the objectives of this study. Examples of these other data elements could include non-opioid medication information, prescribing information, and/or dispensing information.

8.0 STUDY PROCEDURES

8.1 Overview of Procedures

Table 1 provides an overview of the participant procedures and assessments.

Table 1. Overview of Assessments and Procedures

Form	Done by	Before screening	Screening/ Eligibility	Assessment
Recruitment Tracking	Pharmacy	x		
Interest form	Participant		x	
E-consent	Participant		x	
Self-screening	Participant		x	
Assessment domain: Opioid Use				
Narcotic Score (NS metric)	Appriss			x
WHO ASSIST: <i>opioid items</i> ²	Participant			x
Who ASSIST: <i>adapted opioid Items</i> ⁵³	Participant			x
TAPS 1 / 2 Tool: <i>Prescription drug and prescription opioid items</i> ¹	Participant			x
TAPS 1 / 2 Tool: <i>Illicit drug and heroin items</i> ¹	Participant			x
Prescription Opioid Misuse Index ⁵	Participant			x
Overdose Experiences, Self and Witnessed—Drug (OESWD) ⁹	Participant			x
Assessment domain: Substance Use				
WHO ASSIST: <i>Non-opioid drug use items</i> ²	Participant			x
TAPS 1 / 2 Tool: <i>Non-opioid items</i> ¹	Participant			x
Assessment domain: Mental Health				
Patient Health Questionnaire-2 ⁸	Participant			x
Assessment domain: Physical Health				
Short Form-12: <i>General health subscale</i> ⁷	Participant			x
Brief Pain Inventory ⁶	Participant			x
Assessment domain: Demographics				
PhenX demographics: <i>age, education, gender, race, ethnicity, insurance, employment, marital status</i>	Participant			x

8.2 Participant Recruitment and Consent

A convenience sample of adult patients being dispensed opioid prescriptions (including tramadol and not solely receiving buprenorphine or buprenorphine combination products) at any of the participating Kroger Pharmacy locations will be recruited. Recognizing the busy nature of the Kroger Pharmacy environment, we have intentionally designed the recruitment process to require minimal pharmacy staff involvement, requiring staff to only assess the patients' ages and prescription information to target potentially eligible participants. Trained Kroger Pharmacy staff will inform potentially eligible participants of the survey opportunity. Interested patients will be handed a study flyer and an electronic device (e.g., tablet, etc.) with an electronic "interest survey." Study flyers may also be given to customers picking up medications on behalf of others and those

who choose not to initially share contact information. The flyer will only be targeted to those who the pharmacy staff believes are eligible for the study. The flyer will direct interested individuals to a secure web-version of the interest survey. Interested patients will complete the encrypted electronic “interest survey,” which will trigger REDCap to email the patient a link to a secure web-portal containing the e-consent (i.e., an electronic informed consent information sheet that is submitted by participants indicating their consent to participate in the study).

The IRB will be asked to waive the written informed consent requirement because this is a minimal risk study. This study, which includes participants completing on-line self-assessments, could not be practicably carried out if written consent were required. The IRB-approved e-consent information sheet will include a description of all significant elements of the study: what participation entails; risks and benefits of study procedures; alternatives to participation in the study; confidentiality; \$50 payment for participation information; a statement that participation is voluntary and that the participant may withdraw at any time; and information about whom to contact with questions. The e-consent form will also indicate that the decision to participate will in no way influence other aspects of the participant’s treatment, and participants’ data will not be shared with their clinicians.

8.3 Screening

Following submission of the e-consent, the participant will complete the screening self-assessment, and if qualified, the participant will be given access to the health survey.

8.4 Premature Withdrawal of Participants

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

8.5 Study Halting Rules

Given that this study is low risk and does not provide a clinical intervention of any type, it is not anticipated that study will be halted at any time. However, if for an unforeseen reason the study is prematurely terminated or temporarily suspended, the LI, or designee, will promptly inform the respective IRB and sponsor and provide the reason(s) for the termination or temporary suspension. If the study is suspended, the investigative team will work with the appropriate parties to resolve the existing issue in order to reinitiate the study.

8.6 Follow-Up

Participants who complete the e-consent and are eligible for the study but do not complete the health survey within 3 business days will be contacted by study staff and encouraged to complete the survey.

8.7 Participant Reimbursement

Following submission of the completed survey and research staff verifying data are complete with valid answers (valid indicated by response patterns with no or minimal missing values) and are not a duplicate participant submission, participants will be provided with a \$50 prepaid debit card. Partial compensation will not be provided to those who partially complete the survey. Mailing address information for participant compensation will be collected during the survey process.

9.0 STATISTICAL DESIGN AND ANALYSES

9.1 General Design

This study seeks to evaluate the concurrent validity of the NS metric as a clinical measure of opioid risk and establish clinically useful risk-level thresholds relative to the WHO ASSIST. This study also seeks to collect data on the TAPS tool in a large sample of individuals filling opioid medications in order to further validate this instrument in a novel outpatient setting, community pharmacy.

9.1.1 Study Hypotheses

Similar to the “*The TAPS Tool: Screen and Brief Assessment Tool Validation Study, CTN-0059*”, this study will not test any intervention or hypothesis.⁵⁴ This study will focus on the level of agreement between the NS metric and participants' responses to opioid risk assessment questions. The goal of the project is to validate and identify risk cutoffs between the NS metric and the WHO ASSIST. As such, the study is a measurement validation project and so has no primary outcome variables.⁵⁴ See CTN 0093 Statistical Analysis Plan for details.

In addition to analyses involving the NS metric, we will examine the association of the TAPS Tool with the WHO ASSIST risk categories. See CTN 0093 Statistical Analysis Plan for details.

9.2 Rationale for Sample Size and Statistical Power

9.2.1 Projected Number of Sites

This study will involve 15 participating Kroger Pharmacies. Sites will include 12 Kroger Pharmacies in Ohio and 3 rural Kroger Pharmacies in Indiana.

9.2.2 Projected Number of Participants per Site

Survey sample size power estimates are based on the allocation ratio of the national rate of prescription opioid use disorder (POUD) among those prescribed opioid medications in the last year (2.1%,⁵⁵ i.e. 46.6/1). *Thus, the sample is powered to the least prevalent but most severe condition among potential patients.* We calculated an array of sample sizes powered to achieve ≥80% power ($\alpha=0.05$) and 0.70 (“fair”) Area Under the Curve value,^{56,57} using a conservative null hypothesis assumption of 0.5 for discrimination power (Table 2).⁵⁸ Therefore, to ensure the maximum power for the study, we will target recruitment to 1,523 total patients.

Table 2. Power Analyses (AUC=0.70, Discrimination Power=0.5)	
<i>Power</i>	<i>N</i>
0.80	618
0.85	714
0.90	809
0.95	1,047
0.98	1,523

Each Kroger pharmacy site will be responsible for approaching approximately 207 patients (~3,105 collectively). Of these, we anticipate 70% will be interested and agree to share their contact information.³¹ Of these, based on our current research among this population (NCT03149718), we anticipate 70% will actually provide e-consent and complete the survey. Therefore, each site will refer approximately 102 patients who will complete the e-consent and

survey. We will calculate the survey response rate based on the number of potential participants who submit contact information compared to the survey completion rate.

9.3 Statistical Methods for Primary and Secondary Outcomes

A series of a priori analyses will be conducted to evaluate the validity of the NS metric relative to the widely validated gold standard WHO ASSIST and to identify cutoff thresholds. A priori analyses will involve conducting Receiver Operating Curve Analyses (ROC; i.e., sensitivity and specificity, area under the curve [AUC]) to identify clinical cutoff values for the NS metric and low, moderate, and high WHO ASSIST scores. We will also conduct correlational, regression, and Cohen's Kappa statistical analyses to evaluate the relationship between the NS metric and the WHO ASSIST.

We will also conduct exploratory correlational, regression, and Cohen's Kappa statistical analyses to validate the relationship between the NS metric and measures of opioid medication misuse as well as history of opioid overdose. Exploratory ROC, correlational, regression, and Cohen's Kappa statistical analyses between the WHO ASSIST and the TAPS Tool will also be conducted. Considerations in determining the statistical approach can be found in the CTN-0093 Statistical Analysis Plan.

9.4 Significance Testing

The analyses will be conducted using a two-sided test with a type I error rate of 5%.

9.5 Missing Data and Dropouts

This study does not include follow-up assessments, and all study assessments will be completed during the electronic health assessment survey. 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. The completer population, defined as participants who complete opioid outcome score contributing items on the WHO ASSIST and TAPS tool, will be used for the main analysis. Completers also must have NS metric scores. Multiple imputation will be conducted for missing covariates, but missing key outcome data will not be imputed. See CTN 0093 Statistical Analysis Plan for details.

9.6 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for enrolled participants. Descriptive summaries of the distribution of continuous baseline variables will be presented, with measures of central tendency. Categorical variables will be summarized in terms of frequencies and percentages. In addition, analyses will be conducted on the primary and exploratory aims for male and female gender subgroups. See CTN-0093 Statistical Analysis Plan.

10.0 REGULATORY COMPLIANCE, REPORTING AND MONITORING

10.1 Regulatory Compliance

This study will be conducted in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Regulations for the Protection of Human Subjects codified in the International Council for Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements. Written approval for the study protocol, e-consent form, other supporting documents, and any advertising for participant recruitment will be provided to the participating University sites and Kroger recruitment sites by the Institutional Review Board (IRB) of record prior to participation in the study. Any amendments to the protocol or e-consent materials must be approved by the IRB of record before they are implemented. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures. Annual progress reports will be submitted to the IRB, according to its usual procedures.

This study will be registered and updated as needed in ClinicalTrials.gov.

10.2 Statement of Compliance

This study will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Regulations for the Protection of Human Subjects codified in the International Council for Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements. Institutional Review Board Approval

Per NOT-OD-16-094, the University of Cincinnati IRB (UC IRB) will be the IRB of record for the protocol and will provide study oversight in accordance with 45 CFR 46. Participating institutions have agreed to rely the University of Cincinnati and have entered into reliance/authorization agreements for Protocol CTN 0093. The University of Cincinnati will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution, see Single Site IRB (sIRB) Plan.

Prior to initiating the study, university site investigators will obtain written IRB approval to conduct the study at their respective site, see sIRB Plan. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve the e-consent form, recruitment materials, and any materials given to the participant, and any changes made to these documents throughout study implementation. For changes to the e-consent form, a decision will be made regarding whether previously enrolled participants need to be re-enrolled. IRB continuing review will be performed annually, or at a greater frequency contingent upon the complexity and risk of the study. Each site principal investigator is responsible for maintaining copies of all current IRB approval notices, IRB-approved e-consent documents, and approval for all protocol modifications. These materials must be received by the investigator prior to the initiation of research activities at the site, and must be available at any time for audit.

10.3 Informed Consent

The consent process is a means of providing study information to each prospective participant and provides an opportunity for an informed decision about participation in the study. Because this study is minimal risk, involving on-line completion of a survey at one time point, an altered

consent process will be utilized. Specifically, participants will access an IRB-approved electronic informed consent information sheet (i.e., e-consent) and indicate their consent to participate by selecting “continue” at the end of the sheet. The e-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 rights and welfare of the participants will be communicated by emphasizing that the quality of their medical care or pharmacy services will not be adversely affected if they decline to participate in this 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.

10.4 Quality Assurance Monitoring

In accordance with federal regulations, the study sponsor is responsible for ensuring proper monitoring of an investigation and ensuring that the investigation is conducted in accordance with the protocol. Qualified local monitors will oversee participating University sites to ensure they are operating within the confines of the protocol and in accordance with GCP. Monitoring includes, but is not limited to, protocol compliance, documentation auditing, and reporting safety events. Non-conformity with protocol and federal regulations can be reported as a protocol deviation and submitted to the study sponsor and study IRB for further review. Reports will be prepared following monitoring reviews and forwarded to the investigative team and NIDA CCTN. If the monitor’s review indicates that additional training of site study personnel is needed, QA personnel will undertake or arrange for that training. Monitoring will occur not more than quarterly and not less than annually. Details of QA and data monitoring are found in the study QA Monitoring Plan.

10.5 Participant and Data Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. 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/Privacy Board, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees.

To further protect the privacy of study participants, the lead investigator will obtain a federal Certificate of Confidentiality (CoC) from NIH, which protects identifiable research information from forced disclosure and will distribute it to all sites when received. This protects participants against disclosure of sensitive information (e.g., drug use). The CoC allows the investigator and others who have access to research records to permanently refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level, excepting certain circumstances.

By protecting researchers and institutions from being compelled to disclose information that would identify research participants, CoCs help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants. The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating sites will be notified if CoC revision is necessary. Participant records will be held confidential by the use of study codes for identifying participants on electronic case report forms (eCRF), secure storage of any encrypted documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

10.6 Financial Disclosure/Conflict of Interest

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 confirm to the sponsor annually that they have met their institutional financial disclosure requirements.

10.7 Performance Monitoring

OVN and University of Utah leadership will develop a Performance Monitoring Plan. This plan will detail, according to the study timeline, progress the study will make to accomplish its goals. The plan will include the development of performance metrics and will likewise detail procedures and guidance for underperforming recruitment sites. Performance metrics will be assessed in regularly scheduled study meetings (not to occur more than weekly and less than monthly). For these meetings, a performance summary report will be made available to the research team. By pharmacy site, the report will include information such as:

- Number of initiated vs. completed interest surveys
- Number of completed interest surveys vs. expected by study timeline
- Number of initiated vs. completed e-consent forms
- Number of completed e-consent forms vs. expected by study timeline
- Number of initiated vs. completed self-screening forms
- Number completed self-screening forms vs. expected by study timeline
- Description of reasons potential participants are screened as ineligible
- Number of initiated vs. completed health assessment surveys
- Number of completed health assessment surveys vs. expected by study timeline

Based on the team's regular comparison of these metrics by pharmacy recruitment site, low performing sites will be identified. Procedures for improvement of low performing sites will include actions such as:

- Discussion of the site's performance with Kroger Corporate, Regional, and local management.
- Performing on-site visits to discuss performance issues, identify barriers, and make plans to increase performance.
- Discussion and planning with research staff regarding outreach to participants with initiated and uncompleted forms.
- Identification of possible additional Kroger pharmacy sites for outreach advertisement

10.8 Inclusion of Women and Minorities

The study sites should aim and take steps to enroll a diverse study population. Noted in section 2.3 of the study appendix, based on our previous research on this topic, we anticipate 57% of our sample will be female, and 43% will be male. Assessments captured (i.e., TAPS Tool alcohol subscale) are specified for male vs. female respondents. We also anticipate our study sample will approximate the racial/ethnic distributions of the local areas in which the recruitment stores operate. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings and plans to correct these difficulties will be put into place.

10.9 Prisoner Certification

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. This study will not recruit individuals meeting this definition.

10.10 Regulatory Files

Essential documents are those documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating University site for regulatory document compliance prior to study initiation, throughout the study according to regularly agreed upon schedule (not more than quarterly and less than annually), as well as at study closure by local research staff and quality monitors, see section 10.4.

10.11 Records Retention and Requirements

Research records for all study participants are to be maintained by the participating University site investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with IRB, state and federal requirements, whichever is longest. The sponsor and Lead Investigator must be notified in writing and acknowledgment must be received by the participating University site prior to the deletion or relocation of research records.

10.12 Reporting to Sponsor

The investigative team agrees to submit accurate, complete, legible and timely reports to the Sponsor, as instructed by the sponsor. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the study or increase risk to study participants. Safety reporting will occur as previously described. At the completion of the study, the Lead Investigator will provide a final report to the Sponsor.

10.13 Audits

The Sponsor has an obligation to ensure that this study is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance. The LI and authorized staff from the participating research institutions; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); and other agencies such as the Department of Health and Human Services (HHS), the Office for Human Research Protection (OHRP), and the Institutional Review Board of record may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

10.14 Study Documentation

Each participating University site will maintain appropriate study documentation (including research records) for this study, in compliance with ICH E6 and regulatory and institutional

requirements for the protection of confidentiality of participants. Study documentation includes sponsor-investigator correspondence, signed protocol and amendments, Ethics Review Committee or Institutional Review Board correspondence, and approved e-consent document. As part of participating in a NIDA-sponsored study, each site will permit authorized representatives from NIDA and regulatory agencies to examine (and when permitted by law, to copy) records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

10.15 Protocol Deviations

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate within a reasonable period of time following their discovery. Those corrective action plans may be reviewed/approved by the Lead Node with overall approval by the IRB of record. All 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 study. All protocol deviations will be recorded in a REDCap form developed for this project.

Additionally, each site is responsible for reviewing the IRB of record's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

10.16 Safety Monitoring

10.16.1 Data and Safety Monitoring Board (DSMB)

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.

10.17 Training

The CTN-0093 study staff will be trained as specified in the study Training Plan. Training will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP) as well as protocol-specific training on assessments, study procedures, data management, quality assurance, etc.

11.0 DATA MANAGEMENT

11.1 Design and Development

The OVN and University of Utah will be responsible for development of eCRFs, development and validation of the study database, ensuring data integrity, and training site and participating research staff on applicable data management procedures. The remainder of this section provides an overview of the Data Management Plan associated with this protocol.

11.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the OVN and University of Utah and outlined in the Data Management Plan. Given the fact that data in this study are entered remotely by study participants following contact with the pharmacy recruitment sites, limited responsibilities are designated to these sites. However, one important note regarding the Data Management Plan is that it will include procedures, for example, regarding how Kroger staff will capture: if patients were informed about the study and how they were informed about the study. The Plan will also discuss, for example, how these data will be shared on a scheduled basis with OVN and the University of Utah for assessing sampling bias.

11.3 Data Center Responsibilities

The OVN and University of Utah will collaborate to 1) develop a Data Management Plan and will conduct data management activities in accordance with that plan, 2) provide guidance for 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) conduct any preliminary analysis data cleaning activities as needed, and 6) conduct final study data cleaning.

11.4 Data Collection

The data collection process consists of direct data entry at the recruitment pharmacies and/or by participants into the REDCap forms and surveys. Data entry into REDCap should be completed according to the instructions provided and project specific training. Assessments programmed in REDCap will use validation rules, integrity checks, and hard stops as needed to ensure that data are as complete and accurate as possible. For instance, validity checks will employ skip logic to ensure certain item sets are not available to respondents once initial responses are given (e.g., alcohol consumption questions will not be available to those who report they do not drink). Regarding completeness of responses, all survey response sets will require every item to be answered in order to complete the survey. However, to preserve participants' rights to not respond to any item they wish, the response set will include an option that will allow the participant to indicate they wish to not respond to the item. This process will ensure survey data completion with minimal missing values. Furthermore, given that data are entered directly into the REDCap survey by participants without requiring interviewing or data transcription by research staff, we anticipate a high level of validity and accuracy (absence of data entry errors) in this project.

11.5 Data Merge

Data collected in the health survey from study participants will be regularly merged with NS metric data from Appriss Health. OVN and University of Utah staff will securely share participant contact information, dispensing pharmacy, and demographic information with Appriss who will deterministically link NS metric data. Linked data will be returned from Appriss to the OVN and the University of Utah.

11.6 Data Acquisition and Entry

Completed forms and electronic data will be entered into REDCap in accordance with the instructions provided by the OVN and University of Utah. Only authorized individuals shall have access to eCRFs.

11.7 Data Transfer/Lock

Data will be transmitted by the OVN and the University of Utah to the NIDA central data repository as requested by NIDA. The OVN and University of Utah 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. We will comply with the following policy regarding the preparation and transfer of the study data:

“Data from CTN trials are posted 18 months after the final database lock or after the primary manuscript is published, whichever comes first. All of the data are de-identified, and only raw data (i.e., no analysis datasets or derived variables) are provided. Data documentation, consisting of all annotated case report forms (CRFs), the data dictionary, and de-identification notes, is provided to users to assist in data interpretation. Protocol documentation, including a brief study description, the study protocol, and a link to the primary manuscript, is also provided, and users are encouraged to consult these documents for insight regarding proper interpretation of the data.”

11.8 Data Training

The Training Plan for research staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of REDCap.

11.9 Data Quality Assurance

To address the issue of data entry quality, the OVN and University of Utah will follow a Data Management Plan. Data quality summaries will be made available during the course of the protocol, and acceptable quality level prior to study lock or closeout will be established as a part of the Data Management Plan. Data quality will be assessed in regularly scheduled study meetings (not to occur more than weekly and less than monthly). For these meetings, a data quality summary report will be made available to the research team. By pharmacy site, the report will include information, such as:

- Number of interest forms with missing data
- Description of missing data on the interest form
- Number of health assessment surveys with missing data
- Description of missing data on health assessment surveys
- Number of surveys linked to the NS metric
- Description of surveys/participants with unlinked surveys

12.0 PUBLICATIONS AND OTHER RIGHTS

Per NIH policy, the results of the proposed study are to be made available to the research community and to the public at large. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

13.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date
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ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 2.0 of the protocol and agree to conduct this study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- I will ensure that the requirements relating to obtaining e-consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (DHHS), the state, and the IRB.

UNIVERSITY SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date
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University Name _____

Node Affiliation _____

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15.0 APPENDIX: DATA AND SAFETY MONITORING PLAN

Data and Safety Monitoring Plan

1.0 BRIEF STUDY OVERVIEW

Using opioid therapy to treat pain effectively, while minimizing potential adverse consequences, is an important goal. Appriss Health has developed the NS metric, which uses PDMP data on opioid and benzodiazepine prescriptions and aberrant drug behavior (e.g., multiple providers, pharmacies, etc.) to compute a score quantifying the extent of the patient's opioid risk in relation to all prescription opioid users. The association between the NS metric and other indicators of opioid-related risk has not been evaluated, and hence, the degree to which this metric is a useful screening tool is unknown.

The primary objective of this one group, cross-sectional, validation study is to evaluate the concurrent validity of the NS metric as a clinical measure of opioid utilization risk and establish clinically useful risk level thresholds relative to the World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST). A secondary objective of the study is to collect validity data on the Tobacco, Alcohol, Prescription medication and other Substances (TAPS) tool in a large sample of individuals filling opioid pain medications.

Participant Inclusion Criteria

Potential participants must:

1. be dispensed ≥ 1 opioid medication (including tramadol) by a participating Kroger Pharmacy;
2. be ≥ 18 years of age according to Kroger Pharmacy data and self-report

Participant Exclusion Criteria

Potential participants must not self-report:

1. not solely filling buprenorphine or buprenorphine combination products i.e., patients receiving OUD treatment with no other opioid medication use;
2. currently receiving treatment for cancer;
3. having previously completed the survey (this will be re-verified by OVN staff by examining identifying information following health assessment submission);
4. having current involvement with the criminal justice system that has, or could, lead to incarceration

Sample Size

This study will recruit approximately 1,523 participants.

2.0 STUDY MANAGEMENT

1. List of participating enrolling clinics or data collection centers: All potential participants will be Kroger community pharmacy patients dispensed opioid medications.
2. Project timetable: This study will take approximately 24 months to complete. Data collection will require 6-8 months and data analysis will require approximately 3-6 months.

3. **Target population distribution:** As noted above, based on our previous research, we anticipate 57% of participants will be women (n=868). In terms of racial distribution, we anticipate the population will generally reflect that of the states where participants are recruited. The following estimates assume an even distribution of participant recruitment across study sites. For Ohio, we anticipate 82.2% (n=1002) will be white, 12.9% (n=157) black or African American, 2.3% (n=28) Asian, and 2.3% (n=28) from two or more races. Of these, we anticipate 3.8% (n=46) will be Hispanic or Latino. For Indiana, we anticipate 83.9% (n=256) will be white, 9.3% (n=28) black or African American, 2.1% Asian (n=6), and 2.3% from two or more races (n=7). Of these, we anticipate 6.7% (n=20) will be Hispanic or Latino.

3.0 DATA MANAGEMENT AND ANALYSIS

1. **Data acquisition and transmission:** Information for study participants will be obtained from two sources. The first source will be from self-reported responses on REDCap forms, including contact information, demographics, and health information. The second source will be Appriss Health, who will provide the NS metric for all patients enrolled in the study. All research staff will be trained in Good Clinical Practice (GCP) guidelines. In addition, demographic information about all patients informed about the study will be obtained from the participating Kroger pharmacies. Only research staff members directly involved with the study will have access to identifying information for the participants.
2. **Data entry methods:** Demographic and clinical data for study participants will be managed in REDCap, a software toolset and workflow methodology for collection and management of clinical research data developed by Vanderbilt University, in collaboration with institutional partners including the University of Cincinnati Academic Health Center. Only the necessary study personnel will have access to the database.
3. **A priori statistical analysis plan:** Our a priori analyses to identify clinical cutoff values will involve assessing the ability of the NS metric to discriminate between low, moderate, and high-risk opioid use from the WHO ASSIST via receiver operating curve characteristic (ROC) analyses. Area under the ROC curve (AUC) values will be used to determine the accuracy of discrimination threshold levels, and we will identify sensitivity and specificity values balancing low false positive and low false negative rates to determine the NS metric thresholds that classify the specified use thresholds from these opioid measures. Cohen's Kappa Coefficients^{59,60} will be used to evaluate agreement between the identified thresholds and WHO ASSIST risk groups. We will further establish the concurrent validity of the NS metric corresponding to the WHO ASSIST using: Spearman's rho correlation analyses and logistic regression models.⁶¹⁻⁶⁴ Statistical significance values (p<0.05) and magnitudes of correlation and agreement will be used to assess association between indicators. Detailed specifications of study variables and *a priori* and *exploratory* analytical procedures are described in the CTN-0093 SAP.

4.0 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Lead Investigator

The Lead Investigator, with assistance from the Co-Lead Investigator and investigative team, is responsible for study oversight, including ensuring human research subject protection. This study will not use any clinical interventions and there are no expected adverse events during the single on-line completion of the surveys. The only expected risk to participants is a loss of confidentiality, which will be minimized by utilizing an encrypted REDCap platform. Any breach of confidentiality will be reported on a protocol deviation form.

B. Data and Safety Monitoring Board (DSMB)

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.

C. Quality Assurance (QA) Monitoring

Study monitoring will be conducted on a regular basis using local QA monitors. QA monitors will assess compliance with the protocol, GCP requirements, and other applicable regulatory requirements, as well as document the integrity of the study progress. Areas of particular concern will be protocol adherence, IRB reviews and approvals, and regulatory documents. The monitors will interact with the participating University site staff to identify issues and re-train the site as needed to enhance research quality. QA Reports will be prepared by the monitors following each site visit. These reports will be sent to the investigative team and NIDA CCTN. The investigative site will provide direct access to all study related sites (e.g., research office), source data/documentation, and reports for the purpose of monitoring and auditing by local Node monitors, as well as inspection by local and regulatory authorities. See protocol sections 10.4, 10.10, 10.11, and 10.13.

D. Management of Risks to Participants

Confidentiality

Confidentiality of participant records will be ensured by encryption and secure storage of any documents that have participant identifiers as well as secure computing procedures for entering and transferring electronic data. No identifying information will be disclosed in reports, publications, or presentations.

Information That Meets Reporting Requirements

The e-consent document will specify the types of information that are required for reporting and that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

Pregnancy

As there is no medication intervention, pregnancy will not be excluded within the context of this study.

5.0 STUDY SAFETY

Risks:

Breach of confidentiality: As with any study, there is a potential risk of loss of confidentiality. To maintain participant confidentiality, study records and data will be stored in compliance with the International Conference on Harmonization (ICH) guidelines. Participant-reported data will be collected through REDCap, which is HIPAA-compliant and 21 CFR Part 11- ready for audit trails for tracking data manipulation and exports. Emails or text messages between researchers and participants, used in recruitment efforts, will be deleted after information exchange. We will train all study-related personnel to follow HIPAA regulations for research to ensure confidentiality of all data and that the rights of the patients are protected. All data will reside on password-protected encrypted computers, with only the investigators and key members of the research team having access. A variety of other measures will be taken to protect confidentiality, including: We will 1)

assign a unique ID number to each patient, instead of patient names and 2) restrict access to the key linking names and ID numbers to key staff and the PI at each site. Participants will be told that agents of the IRB and QA monitors will be allowed to inspect research records related to this study, if requested.

Emotional Discomfort: The participants may experience some emotional discomfort from answering sensitive and/or personal questions. There is the possibility that the participant will feel bored. The patient's ability to respond to study assessments in the privacy of his/her own home should help in reducing potential emotional discomfort.

Benefits:

Participants may not experience a benefit from participating in this study. Potential benefits include the chance to contribute to a scientific investigation which may benefit other patients like themselves in the future. The risk/benefit ratio is favorable and conduct of the research well justified.

6.0 REGULATORY ISSUES

Reporting of safety concerns to the IRB ad NIDA: The only expected risk to participants is a loss of confidentiality, which will be minimized by utilizing an encrypted REDCap platform. All breaches of confidentiality will be reported to and reviewed by study leadership in regularly scheduled meetings (not to occur more than weekly and less than monthly).

Reporting of IRB action to NIDA: All communications with and actions of the IRB will be kept in a regulatory binder specific for this study. Any protocol changes, amendments, or deviations will be submitted to the IRBs and NIDA and the IRB's actions will then be reported to NIDA. Any other IRB actions will be submitted to NIDA.

Report of changes or amendments to the protocol: All changes and amendments to the protocol will be submitted to the IRBs and NIDA. Only after IRB and NIDA approvals are granted will the changes and amendments be implemented.

Stopping rules: Individual study participants will be informed of their right to discontinue study participation at any time during the study. The PI may discontinue a participant from the study if deemed clinically appropriate. NIDA has the right to discontinue the investigation at any time.

Disclosure of conflict of interest: The investigators have no conflicts of interest.

7.0 DATA MANAGEMENT PROCEDURES

This protocol will utilize a centralized REDCap data capture program. This electronic data capture system (REDCap) will be developed in collaboration by OVN and University of Utah teams to ensure that guidelines and regulations surrounding the use of computerized systems in clinical studies are upheld. Assessments programmed in REDCap will use validation rules, integrity checks, and hard stops as needed to ensure that data are as complete and accurate as possible. See Protocol section 11.4 for additional details.

8.0 DATA AND STATISTICS RESPONSIBILITIES OF THE OVN and UNIVERSITY OF UTAH

The OVN and the University Utah will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) 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) prepare instructions for the use of REDCap and for the completion of eCRFs, 5) conduct ongoing monitoring activities on study data collected from all participating sites, and 6) perform data cleaning activities prior to the final study database lock.

9.0 DATA COLLECTION AND ENTRY

Data will be entered by pharmacy staff and participants into eCRFs through REDCap. Data will be entered into REDCap in accordance with the instructions provided during protocol-specific training and guidelines established by the OVN and the University of Utah. Data entry into the eCRFs is performed by authorized individuals. Mentioned above, assessments programmed in REDCap will use validation rules, integrity checks, and hard stops as needed to ensure that data are as complete and accurate as possible. The investigator at the participating University site is responsible for maintaining accurate, complete and up-to-date research records. See Protocol sections 10.4 and 11.9 that provides overviews of Data Quality Assurance and Quality Assurance Monitoring.

10.0 DATA MONITORING, CLEANING, AND EDITING

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available in REDCap. These reports will be monitored regularly by the OVN and the University of Utah. See Protocol section 11.9 that provides an overview of Data Quality Assurance.

Study progress and data status reports, which provide information on recruitment, availability of primary outcome, regulatory status, and data quality, will be generated regularly and shared with project research leadership and staff.

11.0 DATABASE LOCK AND TRANSFER

At the conclusion of data collection for the study, the OVN and University of Utah will perform final data cleaning activities and will “lock” the study database from further modification. The final analysis dataset will be transferred to the Lead Investigator or designee. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated parties for posting on Datashare, as well as storage and archiving. We will comply with the following policy regarding the preparation and transfer of the study data:

“Data from CTN trials are posted 18 months after the final database lock or after the primary manuscript is published, whichever comes first. All of the data are de-identified, and only raw data (i.e., no analysis datasets or derived variables) are provided. Data documentation, consisting of all annotated case report forms (CRFs), the data dictionary, and de-identification notes, is provided to users to assist in data interpretation. Protocol documentation, including a brief study description, the study protocol, and a link to the primary manuscript, is also provided, and users are encouraged to consult these documents for insight regarding proper interpretation of the data.”

DSM PLAN ADMINISTRATION

Responsibility for data and safety monitoring: the study Lead Investigators will be responsible for the safety monitoring of the study participants.

Frequency of DSM reviews: The study protocol will be reviewed by the CCTN Protocol review Board before recruitment starts. Breaches of confidentiality will be reviewed by study leadership in regularly scheduled meetings for the duration of the study. DSM reports will be submitted to the IRBs and NIDA annually.

Content of DSM report: The DSM report will include a brief description of the study and any changes made. Additionally, we will report baseline sociodemographic characteristics, including age, gender, and race of the subjects screened and randomized. We will also report retention rates and the disposition for all study participants. Any quality assurance issues, regulatory issues, and breaches of confidentiality will be included in the report.