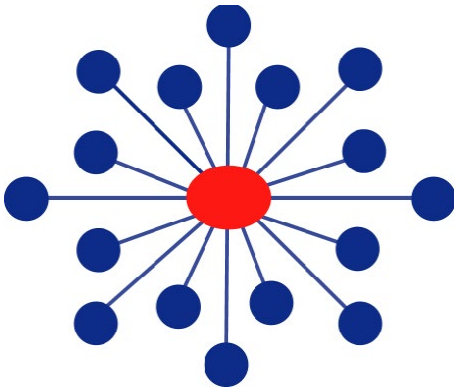

NIDA CTN Protocol 0134

Identifying Regional "Hotspots" and Potential Correlates of Precipitated Withdrawal During Buprenorphine Induction in Fentanyl Users Through Prescriber Survey Responses and Patient Urine Drug Test Results (Buprenorphine-Precipitated Withdrawal Hotspots and Correlates)

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Sponsor: National Institute on Drug Abuse (NIDA)
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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Lead Investigator or other participating study leadership and as consistent with the NIDA terms of award.

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BUP	Buprenorphine
CCTN	Center for the Clinical Trials Network
CFR	Code of Federal Regulations
COWS	Clinical Opiate Withdrawal Score
CTN	Clinical Trials Network
DM	Data Management
DSC	Data and Statistics Center
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HSP	Human Subjects Protection
ICH	International Counfcil for Harmonisation
IRB	Institutional Review Board
LI	Lead Investigator
LN	Lead Node
MH	Millennium Health
MOUD	Medications for Opioid Use Disorder
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OHRP	Office for Human Research Protections

Abbreviation	Definition
OUD	Opioid Use Disorder
OVN	Ohio Valley Node
QA	Quality Assurance
UDT	Urine Drug Test

2.0 PROTOCOL SUMMARY

2.1 Synopsis

Title	Identifying Regional "Hotspots" and Potential Correlates of Precipitated Withdrawal During Buprenorphine Induction in Fentanyl Users Through Prescriber Survey Responses and Patient Urine Drug Test Results
Study Number	CTN-0134
IND Number	N/A
Study Description	This study is a one group, cross-sectional survey study. Active buprenorphine (BUP) prescribers will be recruited to participate in an online survey of clinical program features, characteristics of patients with opioid use disorder (OUD), patients' experience with precipitated withdrawal during BUP induction, and patients' fentanyl use at a single time point. Millennium Health (MH) will provide urine drug test (UDT) results from the counties of prescribers who participated in the survey. Both the survey and UDT results will be obtained from addiction treatment clinics. The UDT results and survey data will be merged at the county level to assess the association between precipitated withdrawal issues and fentanyl, fentanyl analogues, and other drugs of abuse.
Objectives	Primary Objective: Characterize the regional variability in the prevalence of prescriber-reported precipitated withdrawal during BUP induction for individuals using fentanyl and other non- prescribed and/or illicit drugs in approximately 279 counties in the United States. Secondary Objective: Identify potential correlates of precipitated withdrawal in fentanyl users.
Outcome Measures	Primary Outcome Measure: The primary outcome measures for this study are the (1) prevalence of precipitated withdrawal among people with OUD as reported by active BUP prescribers via an online survey and (2) prevalence of fentanyl, fentanyl analogues and other drug positivity rates from patients in the same counties as that of prescribers who participated in the online survey. The results from urine drug tests ordered within the prior six months of initial survey distribution through the survey completion timeframe will be included. Secondary Outcome Measures: Secondary outcomes Smeasures include program characteristics (e.g., location of clinical practice, other medications offered for OUD), characteristics of patients with OUD (e.g., race, insurance type) and buprenorphine induction protocol(s) used by the respondent (e.g., Clinical Opiate Withdrawal Score [COWS] used to start induction in patients, initial BUP dose, etc.).

Study Population	Active BUP prescribers who ordered urine drug test results from MH within the prior six months of initial survey distribution will be eligible to participate in the online survey. MH has an estimated 981 physicians from 602 practices across 279 United States counties who will meet study eligibility criteria.
Phase or Stage	This study is a brief, one-time online anonymous survey.
Description of Research Locations	This study is a partnership between Ohio Valley Node (OVN) academic researchers and MH to detect regional variations and potential risk factors for precipitated withdrawal during BUP initiation. MH is an accredited specialty laboratory with over a decade of experience in medication monitoring and drug testing services, helping clinicians monitor use of prescription medications and illicit drugs and analyzing specimens to identify nationwide drug use trends. MH is certified by the Clinical Laboratory Improvement Amendments and accredited by the College of American Pathologists for high-complexity testing and also holds a HITRUST Cybersecurity Framework Certification to help ensure the security of health care information.
Description of Study Intervention/ Experimental Manipulation	This is a one group, cross-sectional survey study. Aggregated survey data will then be matched at the county level with urine drug test results extracted from data obtained by MH.
Safety Reporting	This study will consist of a one-time online anonymous survey and archival urine drug test results. It is anticipated that it will be deemed as not human subjects by the IRB and, thus, safety reporting is not applicable.
Analyses	Because this topic is newly emerging, this research is primarily descriptive and exploratory in nature; data will be explored to identify potential correlates of precipitated withdrawal, regional variation ("hotspots"), and association between hotspots and fentanyl, fentanyl analogues, or other drug positivity rates including pure fentanyl use. Using logistic regression analyses and other related statistical tools, we will also assess the association between precipitated withdrawal and program characteristics, characteristics of people with OUD and buprenorphine induction protocols used by prescribers.
Study Duration	The estimated time from the start of the enrollment period to survey completion is approximately 6 weeks. After survey completion, the data merge and database lock process will take 2 months. The final report will be submitted to NIDA 4 months after database lock, the primary outcome paper will be submitted to an academic journal 6 months after database lock and the data will be posted on the CTN's Public Data Share 18 months after database lock.

Respondent Duration	The online-survey will be open for approximately 6 weeks. Each respondent will complete the brief survey one time within the 6- week open enrollment period. It is estimated that the survey will take 10 minutes to complete.

3.0 STUDY SCHEMA

- A postcard will be sent to Millennium Health sales team for distribution to selected practices
- An invitation to participate in a brief anonymous REDCap survey will be delivered via email to active buprenorphine prescribers in the Millennium Health network
- Three follow-up reminder emails will be sent at approximately one-week intervals, ideally on a different day of the week than the prior email for optimal participation
- Active buprenorphine prescribers will complete the survey
- At the end of 6 weeks, the survey completion window will close

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- Ohio Valley Node and Millennium Health staff will import initial survey result data into a local data source environment and clean the database and to prepare the data to link with corresponding urine drug test results

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- Data are analyzed and results are reported

4.0 INTRODUCTION

4.1 Study Rationale

Despite the demonstrated efficacy of medications to treat the escalating problem of OUD, such as buprenorphine (BUP), several barriers to implementation exist. It is important to identify barriers that prevent the uptake of medications for opioid use disorder (MOUD) such as BUP, including the rise of fentanyl and fentanyl analogues in the drug supply and its possible association with precipitated withdrawal. Precipitated withdrawal in response to BUP exposure is an acute worsening of withdrawal symptoms, such as abdominal cramps and vomiting, that can discourage the use of BUP treatment. Few studies assess the frequency and characteristics of precipitated withdrawal during BUP induction. The present study will address this knowledge gap by accomplishing two important objectives:

First, this study will characterize the regional variability in the prevalence of prescriber-reported precipitated withdrawal during BUP induction for individuals using fentanyl and other non- prescribed and/or illicit drugs in approximately 279 counties in the United States. This exploratory project will leverage the partnership between the Ohio Valley Node (OVN) and MH, an accredited specialty laboratory specializing in medication monitoring and drug testing services, to survey active BUP prescribers in the MH network about their program characteristics, patient characteristics and BUP induction protocol. These data will provide insight into the prevalence of precipitated withdrawal overall and within specific regions of the United States (i.e., “hotspots”).

Aggregated survey data will then be matched with urine drug test (UDT) results at the county level to accomplish the second objective of the study, which is to identify potential correlates of precipitated withdrawal in fentanyl, fentanyl analogues and other drugs of abuse. MH staff will extract UDT results from the county of prescribers who participated in the survey, then merge UDT results and survey data to assess potential correlates of precipitated withdrawal with fentanyl, fentanyl analogues, and other drug positivity rates. These data will also provide insight into the prevalence of fentanyl, fentanyl analogues, and drugs of abuse positivity rates within specific regions of the United States.

4.2 Background and Significance to the Field

OUD affects 2.7 million people in the United States [1]. In 2020, approximately 75% of all drug overdose deaths involved the use of an opioid [2]. Studies have demonstrated the efficacy of MOUD including methadone and BUP for treating OUD [3,4]; however, several barriers to implementation exist [5,6]. Methadone can only be dispensed by licensed opioid treatment programs, which are highly regulated and have relatively limited availability. BUP, by contrast, is more widely available since it can be prescribed in office-based practices by certified practitioners. Hence, efforts to expand MOUD access have largely focused on increasing the number of BUP practitioners [7]. A potential threat to the forward momentum in the provision of MOUD with BUP is the rise of fentanyl and fentanyl analogues in the drug supply [8]. Fentanyl is lipophilic, enabling it to be sequestered in fat tissue, raising the possibility of an extended period for fentanyl clearance [9]. Evidence of this was found in a recent study in which fentanyl- using individuals continued to test positive for fentanyl an average of 7 days since their last use

[10]. This extended clearance period may contribute to precipitated withdrawal, an acute worsening of withdrawal symptoms (e.g., aches, nausea, vomiting, abdominal cramps, dilated pupils) during

BUP induction [10], which has been reported for some individuals using fentanyl [11, 12].

To date, there is limited understanding of the extent, regional variation, and frequency of precipitated withdrawal during BUP induction. At least anecdotally, precipitated withdrawal is not universally observed in fentanyl users and seems to be more prevalent in some regions of the

US (i.e., “hotspots”), suggesting that other factors play a role. A stronger understanding of precipitated withdrawal among fentanyl users will potentially promote adoption and implementation of BUP, as well as provide additional clinical guidelines for the use of BUP in treating people with OUD. The current study aims to survey active BUP prescribers on patients’ experience of precipitated withdrawal and supplement the survey data with UDT results for fentanyl, fentanyl analogues, and other drug positivity rates from approximately 279 U.S. counties.

Identifying factors that increase the likelihood of precipitated withdrawal will inform treatment approaches and allow clinicians to better predict which of their patients are at heightened risk for experiencing precipitated withdrawal. Findings from this study will assist practitioners in preventing and managing complicated inductions and inform best practices for BUP treatment. Moreover, deeper insights into the induction process may encourage increased adoption of BUP treatment by both practitioners and people with OUD.

4.3 Risk/Benefit Assessment

This study will consist of a one-time anonymous online survey and archival UDT results. No behavioral or pharmacological interventions will be provided in this study. It is anticipated that the IRB will deem this study as not human subjects and, thus, there are no respondents for whom a risk/ benefit assessment is applicable.

5.0 OBJECTIVES

5.1 Primary Objective

The primary objective of this study is to characterize the regional variability in the prevalence of prescriber-reported precipitated withdrawal during BUP induction for individuals using fentanyl and other non-prescribed and/or illicit drugs in approximately 279 counties in the United States. Given this relatively new area of research, this objective is exploratory.

5.2 Secondary Objective(s)

The second objective of this study is to identify potential correlates of precipitated withdrawal in fentanyl users. Similar to the first objective, this objective is exploratory.

5.3 Exploratory Objective(s)

The primary and secondary objectives of this study are exploratory.

6.0 STUDY DESIGN

6.1 Overview of Study Design

In the first phase of this study, we will recruit active BUP prescribers from the MH network to participate in a one-time, cross-sectional, self-administered online anonymous survey.

Respondents will answer questions about program characteristics, characteristics of patients with OUD, and the BUP induction protocol used by the respondent. This design will allow for the recruitment of a geographically diverse sample of active BUP prescribers to provide insights about the prevalence of precipitated withdrawal overall and within specific regions of the United States. The survey responses will also provide data about potential correlates of precipitated withdrawal in fentanyl users (e.g., BUP induction procedures, etc.) and will be merged with UDT results at the county level in the second phase of this study to evaluate the association between precipitated withdrawal and fentanyl, fentanyl analogues, or other drug positivity rates.

In the second phase, we will extract UDT results from the county of prescribers who participated in the survey. Aggregated survey data will then be matched with UDT results at the county level.

6.2 Duration of Study and Visit Schedule

Enrollment is expected to take place over a period of approximately 6 weeks. Respondents will complete an anonymous online survey at a single time point, which will take approximately 10 minutes to complete.

7.0 OUTCOME MEASURES

7.1 Primary Outcome Measure

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

7.1.1 Precipitated Withdrawal

The prevalence of precipitated withdrawal among patients being inducted on BUP will be assessed by asking active BUP prescribers to report the number and percentage of their patients who experience precipitated withdrawal based on prescriber observation and patient report.

7.1.2 Fentanyl and Other Non-Prescribed and/or Illicit Drugs

The prevalence of positive fentanyl, fentanyl analogues, and other drug UDT results from patients in the same counties as that of prescribers who participated in the online survey are primary measures. Urine specimens were analyzed via liquid chromatography-tandem mass spectrometry to detect fentanyl and other non-prescribed and/or illicit drugs.

7.2 Secondary Outcome Measure(s)

7.2.1 Program Characteristics

The survey of active BUP prescribers will include questions about program characteristics, such as the location of clinical practice.

7.2.2 Characteristics of Patients with OUD

The survey of active BUP prescribers will include questions about characteristics of their patients with OUD, such as race and insurance type.

7.2.3 BUP Induction Protocol

The survey of active BUP prescribers will include questions about the BUP induction protocol used by respondents, such as maximum total day BUP dose and the Clinical Opiate Withdrawal Scores (COWS) score. The COWS is an 11-item scale designed to assess the stage or severity of opioid withdrawal and assess the level of physical dependence on opioids.

7.3 Study Timeline

After receiving CCTN approval of the full/final protocol, approximately 2 months of survey preparation activities will elapse prior to commencing survey enrollment. Survey preparation will include refining the survey and recruitment materials/process, applying for and obtaining IRB approval/not human subjects determination, conducting training and developing the data collection systems. Recruitment is expected to take approximately 6 weeks. The survey data will then be merged with UDT results at the county level approximately 1 month after the completion of the last survey. The database will be locked approximately 1 month after the merging process.

8.0 STUDY POPULATION

This is a one-time, cross-sectional, self-administered online anonymous survey. Potential respondents will consist of active BUP prescribers who ordered definitive UDT results from MH within the prior six months of initial survey distribution. Based on data collected between 1/1/2021 and 5/31/2021, our estimated pool of survey respondents will consist of 981 active prescribers from 38 states and approximately 279 counties represented by 602 clinics. All clinics are addiction treatment clinics.

8.1 Strategies for Recruitment and Retention

Active buprenorphine (BUP) prescribers from practices contracting with Millennium Health (MH) for drug testing services will be recruited to participate in the online survey. Potential respondents will consist of active BUP prescribers in addiction treatment clinics who ordered definitive UDT results from MH within the prior six months of initial survey distribution. MH staff have mentioned this potential project to several practices and providers seem to be very interested in this topic. Given the busy schedules of BUP prescribers, we will implement several recruitment strategies to efficiently and effectively recruit as many participants as possible. First, an email will be sent to the MH sales team to ask for their help in informing practitioners at the selected practices about the survey. We will share study postcards, which will include a QR code to increase survey accessibility, with the MH sales team before recruitment starts. Once the survey window opens, the MH Sales team will distribute the postcards to selected practices, including a URL link that prescribers can type in a web browser to access the brief anonymous REDCap survey. An invitation to participate in the survey will also be delivered via email to active BUP prescribers in the MH network. After the initial email is sent to all eligible prescribers by MH, 3 follow-up reminder emails will be sent at approximately one-week intervals, ideally on a different day of the week than the prior email for optimal participation. The survey will be open for approximately 6 weeks. The email will include an “opt-out” link for recipients to decline further participation. During the months the study is enrolling, clinic presentations by MH personnel will include information about the study to encourage clinician participation.

Prescribers will not be reimbursed due to the business relationship between MH and the programs and the brief nature of the survey (i.e., 10 minute completion time). Potential survey respondents will be informed that practices submitting a survey(s) will be provided with study results once they are available.

The IRB will be asked to grant a “not human subjects” determination for the project. Active prescribers will be sent a short recruitment email with the statement that completion of the survey indicates willingness to have their survey responses included in the study data. They will also be informed that their decision to complete the online survey will in no way influence other aspects of their practice.

Retention strategies are not applicable to this study. This study includes a one-time anonymous survey.

9.0 SITE SELECTION

This study does not entail engagement in human subject research and, thus, there are no study sites. This study entails a partnership between OVN academic researchers (specifically from the University of Cincinnati) and MH to detect regional variations and potential factors associated with precipitated withdrawal during BUP initiation.

MH is an accredited specialty laboratory with over a decade of experience in medication monitoring and drug testing services, helping clinicians monitor use of prescription medications and illicit drugs and analyzing specimens to identify nationwide drug use trends. MH is certified by the Clinical Laboratory Improvement Amendments and accredited by the College of American Pathologists for high-complexity testing and also holds a HITRUST Cybersecurity Framework Certification to help ensure the security of health care information.

This study involves a one-time, cross-sectional, self-administered online survey and the use of UDT results that will be merged with the survey data based on county. OVN academic researchers will be responsible for overseeing the entire study and co-developing the online survey with the MH team. Survey respondents will consist of active BUP prescribers who have ordered UDT results from MH. Given that MH team has an established relationship with potential survey respondents, access to contact information for all prescribers who have ordered an UDT result from their lab, and the ability to extract, merge and analyze their archival UDT data with survey data, a partnership between OVN and MH was created to meet the objectives of this study.

10.0 STUDY PROCEDURES

10.1 Screening Visit

Active BUP prescribers will be sent a short recruitment email with the statement that completion of the survey indicates willingness to participate in the survey. Prescribers will also be informed that their decision to participate in the anonymous online survey will in no way influence other aspects of their practice. After reading the invitation email, the prescriber will complete the screening self-assessment. Given that the MH Team will only send email invitations to the list of all practitioners who ordered UDT results within the prior six months of initial survey distribution, one screener question will assess if the potential respondent is a BUP prescriber for OUD. If the prescriber responds in the affirmative, s/he will be given access to the electronic survey for completion. The one-time survey will take 10 minutes to complete.

10.2 Study Halting Rules

Given that this study will not provide a clinical intervention of any type and the minimal risks associated with survey studies, along with the short duration of the project, it is not anticipated that this study will be halted at any time.

10.3 Follow-Up

Given the anonymity of the online survey, there will be no follow up with respondents. Given that automatic email reminders will be sent on a weekly basis during the 6-week survey window, it is our hope that the email will also remind respondents who started the survey but did not complete it during their initial session to finish completing the survey. The survey will take approximately 10 minutes to complete to increase the chances that respondents will complete the survey shortly after they gain full access to the survey questions.

This one-time survey data will then be merged with UDT results at the county level to accomplish the second objective of the study, as described in section **5.2 Secondary Objective.**

10.4 Respondent Reimbursement

Respondents will not be reimbursed due to the business relationship between MH and the programs outside of this research project and the brief nature of the survey (i.e., 5-10 minute completion time).

11.0 STUDY ASSESSMENTS

Unlike a clinical intervention, this study will consist of a one-time electronic survey that will be developed by the OVN and MH research team. The selection of questions for this brief survey will be based on the objectives of the study and the feasibility of completion.

11.1 Table of Assessments

The clinician survey is provided in Appendix A. All questions will be self-administered as a one- time electronic anonymous survey. It is estimated that the survey will take approximately 10 minutes to complete.

11.2 Laboratory Assessments

The laboratory assessments will be based on existing lab data provided by the MH team. Specimens are analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The LC-MS/MS testing method is a laboratory-developed test with performance characteristics determined by Millennium Health, San Diego, California, which is certified by the Clinical Laboratory Improvement Amendments and accredited by the College of American Pathologists for high-complexity testing. We will examine analyte results consistent with either illicit or non- prescribed substance use.

The following drugs will be tested for in patient specimens (metabolites tested in parentheses):

- fentanyl (norfentanyl),
- 4-ANPP,
- 4-fluoroisobutyryl fentanyl,
- 3-methyl fentanyl,
- acetyl fentanyl (acetyl norfentanyl),
- carfentanil,
- butyryl fentanyl,
- acryl fentanyl,
- cyclopropyl fentanyl,
- furanyl fentanyl,
- methoxyacetyl fentanyl,
- U-47700 (N-desmethyl U-47700). heroin (6-MAM)
- morphine
- oxycodone (oxycodone, noroxycodone, oxymorphone),
- hydrocodone (hydrocodone, norhydrocodone, hydromorphone),
- methadone (methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine),
- cocaine (benzoylecgonine),
- methamphetamine
- marijuana (delta-9-tetrahydrocannabinol carboxylic acid),
- gabapentin,
- tramadol (tramadol, N-desmethyl-tramadol, O-desmethyl-tramadol),
- benzodiazepines (alpha-hydroxyalprazolam, 7- amino-clonazepam, nordiazepam, oxazepam,temazepam, lorazepam).

Fentanyl, acetyl fentanyl, and U-47700 are considered positive if either the parent analyte or metabolite is positive. While U-47700 is not a fentanyl analogue, it is a novel synthetic opioid that tends to be grouped with fentanyl analogues based on its similarity in structure and pharmacologic effects. If any parent analyte or metabolite within a drug class is detected, the drug or drug class is considered positive for that specimen. Fentanyl analogue tests are only performed for the fentanyl-positive population. This testing strategy is based on extensive analytical and clinical validation performed at Millennium Health, where it was determined that fentanyl analogues are found in fewer than 0.11% of samples negative for fentanyl.

12.0 TRAINING REQUIREMENTS

12.1 Overall

The CTN-0134 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 study procedures, data management, quality assurance, and any other overall best practices that are relevant to the conduct of this survey study.

13.0 STATISTICAL DESIGN AND ANALYSES

13.1 General Design

This exploratory study will evaluate the association between fentanyl and fentanyl analogues and precipitated withdrawal, as well as assess the association of precipitated withdrawal with other factors, such as buprenorphine dose, fentanyl use alone and with other drugs of abuse, and other clinical factors and demographic factors.

13.2 Study Hypothesis

This is an exploratory study with no hypotheses.

13.3 Primary and Secondary Outcomes (Endpoints)

As noted in **Section 7.0 Outcome Measures,** unlike a clinical trial evaluating the impact of an intervention, the present study is exploratory and does not include a traditional outcome measure. The primary measures of interest in this study are the(1) prevalence of precipitated withdrawal among people with opioid use disorder as reported by active buprenorphine prescribers via an online survey and the (2) rate of fentanyl and other drugs of abuse positivity and co-positivity in urine drug test results from patients in the same counties as that of prescribers who participated in the online survey.

Secondary Outcome Measures: Secondary outcomes measures include program characteristics (e.g., location of clinical practice, other medications offered for opioid use disorder), characteristics of patients with opioid use disorder (e.g., race, insurance type) and buprenorphine induction protocol used by the respondent (e.g., Clinical Opiate Withdrawal Score [COWS] used to start induction in patients, maximum total day buprenorphine dose).

13.4 Statistical Methods for Primary and Secondary Outcomes

Because this topic is newly emerging, this research is primarily descriptive and exploratory in nature; data will be explored to identify potential correlates of precipitated withdrawal, regional variation (“hotspots”), and association between hotspots and fentanyl use. As part of our analysis, we will provide descriptive statistics (e.g. sample size (n), mean (SD), median (IQR)) that outline both UDT and survey results, stratified by geographical region. In addition, UDT positivity and co-positivity rates (by fentanyl) will be stratified by important survey result variables and descriptive statistics will be tabulated and reported. Using logistic regression analyses and other related statistical tools, we will also assess the association between precipitated withdrawal and program characteristics, characteristics of patients with OUD and BUP induction protocols used by prescribers. For example, we will assess the association between the maximum total day BUP dose and precipitated withdrawal [13]. Moreover, consistent with a recent study from the Millennium Health team on the prevalence of fentanyl analogues in 181 counties [14], we will compare the prevalence of fentanyl analogues with the extent of precipitated withdrawal issues reported by practitioners in each county. We will also evaluate the impact of prevalence of other drugs of abuse and their association with precipitated withdrawal. We will also be exploring combinations of drugs in the opioid supply. Methods will include, but are not limited to, fentanyl co-positivity rate analysis for the different analytes of interest, non-supervised cluster-based classification of poly-substance positivity (e.g. K-means) and latent class analysis.

13.5 Demographic and Baseline Characteristics

This study is a one-time anonymous electronic survey. Descriptive summaries of program characteristics from survey respondents will be presented with means and standard deviations. The categorical variables will be summarized via frequencies and percentages.

14.0 REGULATORY COMPLIANCE, REPORTING AND MONITORING

14.1 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. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the except where necessary to eliminate an immediate hazard(s) to respondents.

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.

14.2 Institutional Review Board Approval

Prior to initiating the study, UC investigators will obtain written documentation from the Institutional Review Board (IRB) stating that the project is non-human subjects research.

14.3 Quality Assurance Monitoring

The REDCap survey feature validation rules reduce the likelihood of incorrect values being entered.

14.4 Respondent and Data Confidentiality

The data include responses to an anonymous survey and de-identified UDT results provided at a county level.

Authorized representatives of the sponsor or funding agency may inspect all documents and records required to be maintained by the investigator, including but not limited to, survey data and archival UDT results. The study site will permit access to such records.

By signing the protocol signature page, the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence.

14.5 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.

14.6 Inclusion of Women and Minorities

Given the anonymity of the electronic survey in this study, the study team will not collect demographic data about respondents.

14.7 Regulatory Files

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

14.8 Records Retention and Requirements

Research records are to be maintained by the 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 state and federal requirements. The Sponsor and Lead Investigator (LI) must be notified in writing and acknowledgment from these parties must be received by the site prior to the destruction or relocation of research records.

14.9 Reporting to Sponsor

The principal investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. 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 respondents.

Safety reporting will occur as previously described. At the completion of the study, the LI will provide a final report to the Sponsor.

14.10 Audits

The Sponsor has an obligation to ensure that this study is conducted according to good clinical research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the OVN; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as HHS may inspect research records for verification of data.

14.11 Study Documentation

UC will maintain appropriate study documentation (including research records) for this study Study documentation includes all survey data and deidentified archival UDT data. As part of participating in a NIDA-sponsored study, UC 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.

Source documents include all reports and records necessary for the evaluation and reconstruction of the study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

14.12 Protocol Deviations

This protocol defines a protocol deviation as any noncompliance with the protocol. The noncompliance may be either on the part of the respondent, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

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 respondent. Major protocol deviations are departures that may compromise the respondent safety, respondent 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. UC will be responsible for developing corrective action plans for both major and minor deviations as appropriate. All protocol deviations will be monitored at UC 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.

15.0 DATA MANAGEMENT

15.1 Design and Development

The OVN will be responsible for the development of the study survey, development and validation of the study database, ensuring data integrity, and training 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.

15.2 Site Responsibilities

This single-site study will be conducted by OVN. OVN will partner with MH to conduct the survey and merge survey data and UDT results from active buprenorphine prescribers. OVN will be responsible for management of survey data collected via REDCap. MH is responsible for the management of UDT data. Urine drug testing results are maintained in an Amazon Cloud-based Snowflake data lake which consists of data sources for drug testing results and associated patient specimen characteristics. Demographic characteristics include the location (county/state) of the ordering clinical practice associated with each specimen result.

15.3 Data Center Responsibilities

The OVN will actively carry out the Data Management Plan, provide guidance for survey data that will be collected during the study, develop data dictionaries, conduct data monitoring activities during the open survey window, and conduct data cleaning activities. MH data base systems (snowflake data lake) are maintained by MH staff. Data descriptions (dictionaries) will be developed and provided by MH. MH is responsible for data QA and validation prior to conducting the analyses and final database lock.

15.4 Data Collection

The data collection process will take place via a one-time REDCap survey. REDCap survey questions will be entered according to the instructions provided and project specific training. The survey will use validation rules, integrity checks and hard stops as needed to ensure that the data are accurate and complete. For example, validity checks will employ skip logic to ensure certain item sets are not available to respondents once initial responses are given. The survey will also include options that will allow respondents to indicate that they wish not to respond to the item. The data will be entered directly into REDCap without requiring interviewing or data transcription by research staff. Archival UDT results will be collected from the Snowflake data lake database. The MH data platform supports HIPAA, HITRUST, SOC 1 and 2 Type II, PCI DSS, and FedRAMP (medium) security requirements. The data platform contains de-identified results. Data from the REDCap survey and archival UDT results will be merged at the county level in this project.

15.5 Data Acquisition and Entry

Data will be obtained from a REDCap survey and UDT results supplied by MH. The REDCap survey will include general non-identifying questions about BUP prescribers' patients. UDT data will not include any identifying information about patients or clinical sites.

15.6 Data Editing

Data will be monitored for completeness and accuracy throughout the open survey window. Dynamic reports listing missing values are available in REDCap. These reports will be monitored by OVN.

15.7 Data Transfer/Lock

At the conclusion of data collection for the study, the OVN will perform final data cleaning activities and will lock the study database from further modification. The final dataset will be transferred to the LI. De-identified versions of the dataset will be provided to the NIDA CCTN-designated parties for posting on the CTN DataShare. We will comply with the following policy:

> "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."

15.8 Data Training

The CTN-0134 study staff will receive protocol-specific training on study procedures, data management, quality assurance, etc.

15.9 Data Quality Assurance

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. Non-conformity with protocol and federal regulations can be reported as a protocol deviation and submitted to the study sponsor and for further review. The team will follow the data management and training plans to ensure the highest level of data integrity and quality.

16.0 DATA SHARING, PUBLIC ACCESS AND PUBLICATIONS

This study will comply with the NIH Data Sharing Policy and Implementation Guidance (https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm).

Primary data for this study will be available to the public in the NIDA data repository, per NIDA CTN policy. For more details on data sharing please visit https://datashare.nida.nih.gov/.

The primary outcome(s) publication will be included along with study underlying primary data in the data share repository, and it will also be deposited in PubMed Central http://www.pubmedcentral.nih.gov/ per NIH Policy (http://publicaccess.nih.gov/).

The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

17.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 7.0 of the protocol and agree to conduct this clinical 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 informed 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 (HHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

18.0 PROTOCOL AMENDMENT HISTORY

The table below is intended to briefly capture changes of IRB-approved versions of the protocol, including a description of the major change(s) and rationale (only the most meaningful, substantial changes to the protocol should be documented here). Use of this table is recommended, but not required.

Version	Date	Description of Change	Brief Rationale

19.0 REFERENCES

1. Substance Abuse and Mental Health Services Administration. (2020). *Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health* (HHS Publication No. PEP20-07-01-001, NSDUH Series H-55). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/
2. Provisional Drug Overdose Death Counts. National Center for Health Statistics. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose- data.htm.
3. Shulman, M., Wai, J. M., & Nunes, E. V. (2019). Buprenorphine treatment for opioid use disorder: An overview. *CNS drugs*, 1-14.
4. Toce, M. S., Chai, P. R., Burns, M. M., & Boyer, E. W. (2018). Pharmacologic treatment of opioid use disorder: A review of pharmacotherapy, adjuncts, and toxicity. *Journal of Medical Toxicology*, *14*(4), 306-322.
5. Andrilla, C. H. A., Coulthard, C., & Larson, E. H. (2017). Barriers rural physicians face prescribing buprenorphine for opioid use disorder. *The Annals of Family Medicine*, *15*(4), 359- 362.
6. Haffajee, R. L., Bohnert, A. S., & Lagisetty, P. A. (2018). Policy pathways to address provider workforce barriers to buprenorphine treatment. *American Journal of Preventive Medicine*, *54*(6), S230-S242.
7. Winhusen, T., Walley, A., Fanucchi, L. C., Hunt, T., Lyons, M., Lofwall, M., ... & Chandler, R.K. (2020). The opioid-overdose reduction continuum of care approach (ORCCA): evidence- based practices in the HEALing communities study. *Drug and Alcohol Dependence*, *217*, 108325.
8. Bisaga, A. (2019). What should clinicians do as fentanyl replaces heroin? *Addiction, 114*(5), 782-783.
9. Comer, S. D., & Cahill, C. M. (2019). Fentanyl: Receptor pharmacology, abuse potential, and implications for treatment. *Neuroscience & Biobehavioral Reviews*, *106*, 49-57.
10. Huhn, A. S., Hobelmann, J. G., Oyler, G. A., & Strain, E. C. (2020). Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug and Alcohol Dependence*, *214*, 108147.
11. Randhawa, P. A., Brar, R., & Nolan, S. (2020). Buprenorphine–naloxone “microdosing”: an alternative induction approach for the treatment of opioid use disorder in the wake of North America’s increasingly potent illicit drug market. *Cmaj*, *192*(3), E73-E73.
12. Antoine, D., Huhn, A. S., Strain, E. C., Turner, G., Jardot, J., Hammond, A. S., & Dunn, K. E. (2021). Method for successfully inducting individuals who use illicit fentanyl onto buprenorphine/naloxone. *The American Journal on Addictions*, *30*(1), 83-87.
13. Quattlebaum, T. H., Kiyokawa, M., & Murata, K. A. (2021). A case of buprenorphine- precipitated withdrawal managed with high-dose buprenorphine. *Family Practice*.
14. Stanton, J. D., Whitley, P., LaRue, L., Bundy, W. L., Dawson, E., & Huskey, A. (2020). Fentanyl analog positivity among near-real-time urine drug test results in patients seeking health care. *Drug and Alcohol Dependence*, *217*, 108264.

20.0 APPENDIX A: SURVEY

E-mail to Providers [To be sent by Millennium Health]

Dear Buprenorphine Prescribers,

As a buprenorphine prescriber with firsthand knowledge of how fentanyl may have affected your clinical practice, we are inviting you to participate in a short, anonymous survey that will be correlated with urine drug testing results at a county level. **If you are an office staff member, we ask that you please forward this email to the buprenorphine prescriber(s) in your practice.**

Millennium Health is partnering with investigators from the University of Cincinnati to conduct a study funded by the National Institute on Drug Abuse (NIDA) to detect regional "hotspots" and potential correlates of precipitated withdrawal during buprenorphine induction in fentanyl users. We currently have only a limited understanding of the extent, regional variation, and frequency of precipitated withdrawal during buprenorphine induction. In addition, not all fentanyl users experience precipitated withdrawal, suggesting that other factors play a role. This research will identify factors that increase the likelihood of precipitated withdrawal, which could inform treatment approaches and allow you to better predict which of your patients are at heightened risk for experiencing precipitated withdrawal. **Your input is essential to help us answer these important questions.**

Please answer questions based on your clinical practice. We will not be tracking individual responses to the survey to maintain anonymity and confidentiality. You can decline to take the survey or choose not to answer specific questions in the survey. We anticipate the survey will take you 10 minutes to complete. Practices submitting a survey(s) will be provided with study results once they are available. By submitting the survey, you are agreeing to have your responses included in the study data. Your decision about completing the survey will in no way influence other aspects of your practice.

This link will take you to the REDCap Survey: [Link]

REDCap Survey

0. Have you prescribed buprenorphine for opioid use disorder (OUD) in the past 6 months?

☐ No ☐ Yes

A. Program Characteristics

For all relevant questions, please assume that the term "buprenorphine" includes buprenorphine/naloxone combination products as well as mono formulations.

A1 Where is your clinical practice located?

State:

County:

City:

A2. Are you affiliated with an academic institution (college/university)?: ☐ No ☐ Yes

A3. Does your clinic offer other medications for OUD?

Methadone?: ☐ No ☐ Yes

Extended-release naltrexone?: ☐ No ☐ Yes

A4. About how many patients with opioid use disorder (OUD) do you prescribe buprenorphine for **per month**? _____

B. Experience with Precipitated Withdrawal During Buprenorphine Induction

This survey asks about your patients' experience of precipitated withdrawal during buprenorphine induction during the last 6 months. We define patient-reported precipitated withdrawal as patient-reported new-onset or worsening withdrawal symptoms following buprenorphine administration. We define observed precipitated withdrawal as any increase in COWS score OR an increase in clinician observed opioid- withdrawal symptoms following buprenorphine administration.

B1. How does YOUR practice define observed buprenorphine-precipitated withdrawal? (Please select all that apply)

☐ An increase in COWS score

☐ An increase in opioid-withdrawal symptoms

☐ Other (Specify):

B2. During the last 6 months, have patients declined buprenorphine treatment due to reported concern about precipitated withdrawal? ☐ No ☐ Yes

B3. Have you made any changes to your buprenorphine induction protocol(s) for patients who self-report use

of fentanyl? ☐ No ☐ Yes [IF NO, SKIP TO B4]

B3.1 Please select all changes made:

☐ An increase in the COWS score needed for induction

☐ An increase in the amount of time since prior use before starting buprenorphine

☐ A change in the initial induction dose of buprenorphine

☐ Other (Specify):

B4. During the last 6 months, have any of your patients experienced precipitated withdrawal based on observation or patient report? ☐ No ☐ Yes [IF NO, SKIP TO SECTION C]

B5. How many patients have you initiated on buprenorphine induction in the past 6 months?_____

B6. During the last 6 months, around what percentage of your patients have experienced precipitated withdrawal based on observation or patient report? _____

B6.1. During the last 6 months, about what percent of these patients experienced precipitated withdrawal based on:

	Estimated%
a. Observation by you during induction	☐ 0% ☐ 1-9% ☐ 10-49% ☐ >50%
b. Patient report during home induction prescribed by you	☐ 0% ☐ 1-9% ☐ 10-49% ☐ >50%
c. Patient report during past buprenorphine induction by other provider(s)	☐ 0% ☐ 1-9% ☐ 10-49% ☐ >50%
d. Patient report when using illicit buprenorphine not supervised by a provider	☐ 0% ☐ 1-9% ☐ 10-49% ☐ >50%

B7. How long ago did your practice begin seeing patients on fentanyl who were experiencing precipitated withdrawal based on observation or patient report?

☐ Less than 6 months; ☐ 6 months to 1 year; ☐ 1 to 2 years; ☐ 2 to 3 years; ☐ 3 to 4 years; ☐ ≥ 5years

B8. What steps have taken when patients have experienced severe precipitated withdrawal? (Check all that apply)

☐ Provided “comfort” (ancillary) medications (i.e., medications to treat withdrawal

symptomatically, such as clonidine)

☐ Sent patient to ER

☐ Had them come into the office

☐ Other (Specify):

C. Buprenorphine Induction Protocol

Microdose/ultra-low dose Protocol

C1. Do you use a "microdose/ultra-low dose" buprenorphine induction protocol (i.e., defined as a starting buprenorphine dose of < 2mg)? No Yes [IF NO, SKIP TO C2]

For the "microdose/ultra-low dose" protocol:

C1.1 What patient characteristics trigger the use of this protocol? Please select all that apply:

☐ Past history of precipitated withdrawal with buprenorphine induction/use

☐ Patient reports fentanyl use/has fentanyl-positive urine drug screen

☐ Patient is on a long-acting opioid (e.g., methadone)

☐ Patient is hospitalized

☐ Patient is medically compromised

☐ Patient is pregnant

☐ Other (Specify):

C1.2 What is the first buprenorphine dose typically used for the "microdose/ultra-low dose" protocol? _____mg

C1.3 Are "comfort" (ancillary) medications offered as part of this protocol? ☐ No ☐ Yes

C1.4 Following the "microdose/ultra-low dose" protocol schedule, how many days does it take to reach a 16 mg dose of buprenorphine: _____days

C1.5 During the last 6 months, what % of patients initiated on buprenorphine have been initiated with the "microdose/ultra-low dose" protocol? ☐ 0% ☐ 1-9% ☐ 10-49% ☐ >50%

C1.6 Approximately what % of participants inducted using the "microdose/ultra-low dose" protocol have been successfully inducted (e.g., reached target dose of buprenorphine for buprenorphine-maintenance)? ☐ 0% ☐ 1-9% ☐ 10-49% ☐ >50%

C.1.7 Approximately what % of participants inducted using the "microdose/ultra-low dose" protocol have experienced precipitated withdrawal? ☐ 0% ☐ 1-9% ☐ 10-49% ☐ >50%

Standard Office-based/Observed Protocol

C2. Do you use a "standard" buprenorphine induction protocol (i.e., defined as a buprenorphine starting dose of ≥2 mg)? ☐ No ☐ Yes [IF NO SKIP TO C3]

C2.1. At what COWS score do you typically start an induction in a non-pregnant patient without renal or

hepatic dysfunction?

- ☐ I do not use COWS scores
- ☐ >8
- ☐ >10
- ☐ >12
- ☐ Other (Specify):

C2.2. For patients using fentanyl, what is the minimum time since last opioid use you typically require before starting buprenorphine in a non-pregnant patient without renal or hepatic dysfunction?

- ☐ No specific minimum time
- ☐ At least 12 hours
- ☐ At least 24 hours
- ☐ At least 36 hours
- ☐ At least 48 hours
- ☐ Other (Specify)

C2.3 What is the first buprenorphine dose (not total first day dose) you typically provide to start an induction for a non-pregnant patient without renal or hepatic dysfunction?

- ☐ 2 mg
- ☐ 4 mg
- ☐ 8 mg
- ☐ 16 mg
- ☐ Other (Specify):

C2.4 What is the maximum total first day buprenorphine dose you will provide to a non-pregnant patient without renal or hepatic dysfunction?

- ☐ 4 mg
- ☐ 8 mg
- ☐ 16 mg
- ☐ 24 mg
- ☐ I do not have a set maximum; I will give as high a dose as is needed.
- ☐ Other (Specify):

C2.5 Are "comfort" (ancillary) medications offered as part of this protocol? No Yes

Home Induction Protocol

C3. Do you use a home buprenorphine induction protocol? ☐ No ☐ Yes [IF NO SKIP TO D]

C3.1. For patients using fentanyl what is the minimum time since last opioid use you typically require before starting buprenorphine in a non-pregnant patient without renal or hepatic dysfunction?

- ☐ No specific minimum time

- ☐ At least 12 hours
- ☐ At least 24 hours
- ☐ At least 36 hours
- ☐ At least 48 hours
- ☐ Other (Specify):

C3.2 What is the first buprenorphine dose (not total first day dose) you typically provide to start an induction for a non-pregnant patient without renal or hepatic dysfunction?

- ☐ 2 mg
- ☐ 4 mg
- ☐ 8 mg
- ☐ 16 mg
- ☐ Other (Specify):

C3.3. What is the maximum total first day buprenorphine dose you will provide to a non-pregnant patient without renal or hepatic dysfunction?

- ☐ 4 mg
- ☐ 8 mg
- ☐ 16 mg
- ☐ 24 mg
- ☐ I do not have a set maximum; I will give as high a dose as is needed.
- ☐ Other (Specify):

C3.4 Are "comfort" (ancillary) medications offered as part of this protocol? ☐ No ☐ Yes

C3.5 During the last 6 months, what % of patients initiated on buprenorphine have been initiated with the home-induction protocol? ☐ 0% ☐ 1-9% ☐ 10-49% ☐ >50%

D. Characteristics of Patients with Opioid Use Disorder (OUD) Presenting for Buprenorphine Treatment

D1. During the last 6 months, approximately how many OUD patients have presented for buprenorphine treatment? _____

D2. These questions ask about self-reported substance use characteristics of OUD patients: a) presenting for buprenorphine treatment; and b) experiencing buprenorphine-precipitated withdrawal during the last 6 months. Please give your "best guess" estimates.

	OUD patients presenting for buprenorphine treatment (Estimated%)	Patients with observed or reported buprenorphine-precipitated withdrawal (Estimated%)
Report using any fentanyl on a regular basis	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
Report using exclusively fentanyl as their only opioid of use	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
Report IV fentanyl/opioid use	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%

D3. These questions ask about urine drug test results of OUD patients: a) presenting for buprenorphine treatment; and b) experiencing buprenorphine-precipitated withdrawal during the last 6 months. Please give your "best guess" estimates.

	OUD patients presenting for buprenorphine treatment (Estimated%)	Patients with observed or reported buprenorphine-precipitated withdrawal (Estimated%)
Have an initial urine drug toxicology test positive for fentanyl	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
Have an initial urine drug toxicology test positive for fentanyl and negative for all other opioids?	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
Have an initial urine drug toxicology test positive for other non-opioid substances	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
Most prevalent non-opioid substance detected on initial urine drug toxicology	☐ Benzodiazepines ☐ Cocaine ☐ Marijuana ☐ Methamphetamine ☐ Other (Specify):	☐ Benzodiazepines ☐ Cocaine ☐ Marijuana ☐ Methamphetamine ☐ Other (Specify):

D4. These questions ask about demographic characteristics of OUD patients: a) presenting for buprenorphine treatment; and b) experiencing buprenorphine-precipitated withdrawal during the last 6 months. Please give your "best guess" estimates.

	OUD patients presenting for buprenorphine treatment (Estimated%)	Patients with observed or reported buprenorphine-precipitated withdrawal (Estimated%)
Most common age	☐ <25 ☐ 25-39 ☐ 40-55 ☐ >55	☐ <25 ☐ 25-39 ☐ 40-55 ☐ >55
Male	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
Hispanic?	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
American Indian/Alaskan Native?	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
African-American/Black?	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
Asian?	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
Native Hawaiian/Other Pacific Islander?	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
White/Caucasian?	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%
More than one race/ Bi-racial?	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%	☐ 0% ☐ 1-25% ☐ 26-50% ☐ 51-75% ☐ >75%

Thank you for your participation!