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Clinical Research Protocol

THE EFFECT OF CHRONIC PAIN ON DELAY DISCOUNTING IN METHADONE PATIENTS

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LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	Analysis of variance
BPRU	Behavioral Pharmacology Research Unit
CFR	Code of Federal Regulations
COWS	Clinical Opiate Withdrawal Scale
DCF	Data collection form
EKG	electrocardiogram
FDA	Food and Drug Administration
GAD	Generalized anxiety disorder
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IM	Intramuscular
IRB	Institutional Review Board
IV	intravenous
MAT	Medication assisted treatment
MLR	Multiple linear regression
MMT	Methadone maintenance treatment
NIDA	National Institute on Drug Abuse
OHRP	Office of Human Research Protections
OTOP	Opiate treatment outpatient program
OUD	Opioid use disorder
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PCS	Pain catastrophizing scale
SAE	serious adverse experience
SCL	Symptom Checklist
SLR	Simple linear regression
SOWS	Subjective Opiate Withdrawal Scale
SUD	Substance use disorders
VAS	Visual analog scale

PROTOCOL SYNOPSIS

TITLE	The Effect of Chronic Pain on Delay Discounting in Methadone Patients
SPONSOR	D. Andrew Tompkins, MD MHS
FUNDING ORGANIZATION	NIDA
NUMBER OF SITES	1
RATIONALE	The epidemic of opioid overdose deaths continues to rise, killing more persons in 2017 than HIV/AIDS at the height of that epidemic. Medication assisted treatment, including methadone and buprenorphine, is the standard of care for the treatment of OUD. However, chronic pain can reduce treatment efficacy during medication assisted treatment and is associated with illicit substance relapse, dropout, and subsequent overdose. Mechanisms by which chronic pain may influence the impulsive decision making (e.g., drug relapse) in persons with OUD have not been well characterized. A better understanding is needed of decision-making in this population. Two factors that can influence decisions to use drugs are impulsivity and acute opioid withdrawal. This proposal will test how chronic pain is associated with increases in impulsive decision making in OUD, whether impulsive decision making is greater when undergoing opioid withdrawal, and how catastrophizing may modify the association between withdrawal and impulsive decision making in patients with chronic pain and OUD. An ideal population for this developmental research project is methadone-maintained patients, who show high treatment attendance rates and will therefore assure study efficiency and reliable completion.
STUDY DESIGN	This proposal is a randomized double-blind placebo-controlled Phase 1 clinical trial / human laboratory study to assess the effect of acute opioid withdrawal precipitated by 0.1 mg IM naloxone on delay discounting in patients on MMT with and without chronic pain.
PRIMARY OBJECTIVE	1. Determine the effect of aversive stressors on delay discounting in persons in methadone maintenance.
SECONDARY OBJECTIVES	2. Investigate the degree to which trait pain catastrophizing modifies the association between opioid withdrawal and delay discounting in the PAIN group. 3. Examine the effect of biological sex on discounting, opioid withdrawal, pain VAS, and pain catastrophizing 4. Examine the association between somatization, depressive symptoms, anxiety and discounting.
NUMBER OF SUBJECTS	We expect to enroll 130 participants on MMT, 65 in the chronic pain group (PAIN) and 65 in the group without chronic pain (NO PAIN). Assuming a 25% drop-out rate, we expect to have 50 completers of both experimental sessions in each group.

SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1) Male and female adults aged 18-65 2) Stable methadone dose (at least 21 days) verified by contacting participant's opioid treatment program 3) Understand and speak English 4) Urine toxicology screen negative for drugs of abuse and positive for methadone 5) Must be without by signs of intoxication as evidenced by ability to receive full dose of methadone prior to research activities 6) Presence of chronic pain (>3 months) for the PAIN group and absence of pain for the NO PAIN group. Exclusion Criteria: 7) Unstable psychiatric illness as assessed by the Mini International Neuropsychiatric Interview (e.g. active suicidal ideation, psychosis) 8) Unstable medical illness as assessed by the study's independent medical monitor (e.g. uncontrolled hypertension, recent myocardial infarction, recent stroke, unstable angina) that may be affected by precipitated withdrawal 9) Prescription opioid use besides methadone 10) Acute pain process unrelated to chronic pain 11) Women who are pregnant or lactating 12) Known allergy to naloxone Patients will be allowed to re-screen if it is expected that an inclusion criterion not met or an exclusion criterion met will change prior to the end of study recruitment.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Naloxone 0.1 mg IM Product will be administered once at the beginning of a study session. Administration will occur two hours after methadone dosing.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Placebo injection (0.9% Normal Saline) Product will be administered once at the beginning of a study session. Administration will occur two hours after methadone dosing.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for an average of two to four weeks **Screening:** 3 hours **Sessions:** Each session will last approximately four hours. Sessions must occur at least 48 hours apart.
CONCOMMITANT MEDICATIONS	Beyond their methadone maintenance dose, participants will be allowed to take OTC or prescription strength non-opioid analgesic medications such as acetaminophen or ibuprofen for pain throughout the study, consistent with standards of care. **Prohibited**: Opioid analgesics other than methadone

EVALUATIONS	
PRIMARY ENDPOINT	• Delay discounting of money rate (k)

SECONDARY ENDPOINTS	• Pain VAS ratings (0-100)
	• Peak COWS
	• Peak SOWS
	• Peak Change from Baseline Pupil Diameter
	• Peak VAS of Subjective drug effects (0-100)
	  • Drug Effects
	  • Good Effects
	  • Bad Effects
	  • Liking
	  • Sick

OTHER EVALUATIONS	• Pain Catastrophizing Scale • Barratt Impulsivity Scale-11 • Eysenck Impulsivity Questionnaire • Sensation Seeking Scale • Zimbardo Time Perspective Inventory
SAFETY EVALUATIONS	• Incidence of adverse events • Change in vital signs from baseline (HR, BP, RR, % oxygen saturation)
PLANNED INTERIM ANALYSES	When approximately 10 patients have completed the study, an interim analysis will be conducted by the study statistician. If there is no trend of differences in delay discounting between placebo and naloxone administration sessions, we would discuss with our NIDA program official and independent medical monitor on the following two options: increasing the dose of naloxone to 0.15 mg or administering 0.1 mg naloxone at trough instead of peak methadone levels. Serious adverse events will be monitored by the medical monitor throughout the duration of the study.
STATISTICS **Primary Analysis Plan**	Using methods developed by co-I Johnson, nonlinear regression will be used to calculate individual values of k, larger k values indicate greater discounting or more impulsiveness. K values are normalized using log transformation for parametric analysis. We will use repeated measures analyses implemented in SAS PROC MIXED. The dependent variable is k (discounting). Independent variables include Group (PAIN vs. NO PAIN), a fixed, between-subjects effect and Condition (control vs. withdrawal), a repeated, within-subjects effect. The Group x Condition interaction will be examined to determine if group differences vary by condition. Planned contrasts will explore additive effects of chronic pain and withdrawal by examining whether discounting by the PAIN group in the withdrawal condition is greater than 1) discounting by the PAIN group in the control condition, or 2) discounting by the NO PAIN group in the withdrawal condition. To examine the effect of differing levels of peak aversive stimuli on discounting, we will conduct analyses using only data from the naloxone-precipitated withdrawal session that include peak COWS

	scores.
Rationale for Number of Subjects	Because there is no empirical data on within-subject changes in discounting associated with naloxone precipitated withdrawal, we estimated change using data from a study by consortium PI Johnson that used similar measures and found abstinence from smoking in nicotine-dependent individuals' decreased discounting rates (*f2*=.02). For between group differences, we relied on data from our pilot study showing a correlation between pain and discounting (rho=.25) consistent with a small to medium effect size (*f2*=.08). Three reported effect sizes for studies comparing opioid and tobacco dependent participants and non-dependent participants show much larger effects sizes (approximately *f2*=0.4). Thus, basing the sample size on the effect size seen in the pilot study conservatively yields a sample size that will provide more than sufficient power to detect a group difference. Using these within-subject and between-subjects effect sizes, and assuming a correlation among repeated measures of 0.5, a final, analysis sample of 100 (50 per PAIN and NO PAIN groups) will provide greater than 80% power to detect significance (alpha=.05, 2-tailed) for between groups main effects, within-subject effects of condition, and the interaction between the two.

1 BACKGROUND

1.1 Background/prevalence of research topic

Chronic pain is pain that has persisted for at least one month past the usual healing time of a specific injury, typically lasting for 6 months or longer (1, 2). Chronic pain is highly prevalent in persons with opioid use disorder (OUD), and is not sufficiently treated by opioid agonist treatment alone. Persons in methadone maintenance treatment (MMT) and office-based buprenorphine treatment for OUD have high rates of clinically significant chronic pain (37-80% depending on the definition) (3-6). Longitudinal studies have shown that chronic pain during MAT is associated with greater ongoing drug use (7-10), treatment drop out (9, 11) and risk of suicide (12) compared to patients without chronic pain. Together, these studies indicate that in MAT, pain is highly prevalent; MAT alone does not provide adequate analgesic relief; and ongoing pain contributes to worse treatment outcomes, including illicit substance use. Little is known about the behavioral/cognitive processes that may be affected by chronic pain, particularly processes associated with relapse while on MAT.

Delay discounting is the relative preference for smaller sooner over larger later rewards, an aspect of impulsivity. Most individuals would prefer an immediate $100 over $100 delayed by 1 year. However, when faced with the choice between receiving $95 now versus $100 in 1 year, preferences for the delayed reward may increase. By assessing such choices across multiple delays, delay discounting quantifies the devaluation of rewards over time, which allows for an index of overall discounting rate. Delay discounting models a fundamental decision in substance use disorders (SUD): the smaller immediate reward of drug euphoria, or the delayed but more valuable rewards of improved functioning and life satisfaction that come with prolonged abstinence (14, 15). The finding that individuals with SUD discount more than individuals without SUD has been shown for multiple drugs (16-21), including opioids (22-24). Effects are large and meaningful. For matched controls without OUD, $1000 lost half its value in 5 years, while it lost 50% of its value in only 6 months for individuals with OUD: a 10-fold difference. Within patients with OUD, greater discounting is associated with increased sharing of injection equipment – an HIV risk factor. Studies in nicotine use disorder show that low delay-discounting predicts success in treatment (25-27), and one study showed a similar trend in MAT (p=.08) (28). Finally, recent research has suggested that aversive states, specifically opioid withdrawal, can further increase rates of discounting (29, 30).

Understanding the cognitive effect of aversive states (e.g. chronic pain) in patients with OUD could provide a potential for time-limited clinical interventions to prevent drug use. One of the seminal researchers in delay discounting (31) has proposed that the attention-focusing property of pain and other aversive stimuli is a result of delay discounting processes (32). Consistent with the hyperbolic bow in the shape of discounting curves (31, 33), pain is postulated to create strong immediate temptation to focus attention on the painful stimulus, at the expense of attention to other consequences, both immediate and delayed. From a cognitive perspective, immediate focus on pain likely leads to a reduced capacity to maintain attention and hold representations of potential future outcomes in

working memory. Indeed, decreased attention and working memory load have been shown in chronic pain patients (34, 35). Little empirical research to date has explored the association between pain and discounting, although similar disruptions in central reward and executive control pathways in both patients with chronic pain and SUD provides strong theoretical basis for an association (36). Additionally, previous research has shown an increase in discounting associated with other aversive states including sleep deprivation (37), and importantly, opioid withdrawal (29, 30). In addition, our recent cross-sectional study showed a significant association between delay discounting of pain-specific consequences and risk for opioid misuse in chronic pain patients (38).

Another critical element in the experience of pain that increases attention to painful stimuli, catastrophizing (39, 40), provides an additional theoretical basis for the association between pain and discounting. Pain catastrophizing is a set of negative emotional/cognitive processes involving rumination and pessimism, perceptions of helplessness, and magnification of pain-related symptoms and is measured by the pain catastrophizing scale (PCS; (40)). Catastrophizing occurs during a painful experience or in anticipation of a painful experience. Research suggests that catastrophizing is directly associated with amplification of pain processing and is an etiologic/prognostic factor in several persistent pain syndromes (41-45). The tendency to and intensity of catastrophizing is relatively stable over time (40, 46, 47). Pain catastrophizing has been relatively unexplored in individuals with OUD, but recent clinical reports suggest catastrophizing may be an important psychological risk factor associated with opioid overdose fatalities (48, 49) and has been associated with craving and risk of opioid misuse in chronic pain patients at risk for OUD (50, 51). Given its importance and prognostic value in other chronic pain populations, this gap surrounding the role of catastrophizing in individuals with OUD and chronic pain needs to be filled. An ideal population to examine these associations are methadone-maintained patients, who show extremely high treatment attendance rates and will therefore assure study efficiency and reliable completion. Promising results would be followed up with an R01 application expanding the research, including extension to patients with OUD on buprenorphine and chronic pain patients on daily prescription opioid therapy without OUD but at risk for opioid misuse. By exploring mechanisms leading to impulsive relapse during aversive stimuli, this research may ultimately lead to targeted behavioral, cognitive, and/or pharmacological interventions that alter impulsivity and prevent relapse.

Provide a brief summary of the non-clinical data that has clinical significance.

2 STUDY RATIONALE

There is a great need to understand the cognitive processes underlying illicit opioid use during methadone maintenance treatment for opioid use disorder, especially in patients with co-occurring chronic pain. Ongoing use is associated with increased risk for opioid overdose, treatment drop out and HIV seroconversion/transmission.

2.1 Risk / Benefit Assessment

The purpose of the study is to conduct a Phase 1 clinical trial / human laboratory study to examine the effect of chronic pain alone and in presence of acute opioid withdrawal on

delay discounting of money in patients on methadone maintenance for the treatment of OUD. Additionally, this project will examine how pain catastrophizing may modify the association of chronic pain and opioid withdrawal on changes in delay discounting of money. If withdrawal and catastrophizing were found to affect impulsive decision making as assessed by delay discounting, future research could extend the study of these variables to determine if they play an explicitly causal role in decisions to use opioids (relapse). Delay discounting may then be shown to serve as a surrogate endpoint in clinical trials assessing primary or secondary prevention of opioid use disorders. Researchers could develop interventions to remediate impulsivity as assessed by delay discounting, thereby preventing relapse and improving the efficacy of opioid use disorder treatment.

There are no direct benefits to the research participant. The research has the potential to improve the lives of future patients with opioid use disorder by improving treatment retention and reducing risk for overdose deaths.

The impulsivity tasks and assessments present no risks exceeding those of normal everyday experiences, although participants may experience boredom, fatigue, or frustration during as a result of these sessions and other assessments.

The main potential risk involves precipitated opioid withdrawal. Opioid withdrawal is distressing to the individual, but is not life threatening. Symptoms may include nausea, vomiting, diarrhea or loose stools, body aches, dysphoric mood, and gooseflesh. Changes to vital signs, including elevations in pulse and blood pressure, may also occur. OTOP staff members are well trained to recognize and treat these symptoms.

There is a small risk of worsening psychiatric symptoms or substance relapse while undergoing precipitated withdrawal. All attempts will be made to screen out vulnerable individuals, and to ensure that no symptoms of pain or withdrawal remain at the end of sessions. If relapse does occur, we will communicate this information to the outpatient opioid treatment program. Consent to contact the program to verify the methadone dose is a pre-requisite for study participation. If need be, referrals can be made for psychiatric or higher levels of substance abuse treatment, including emergency room psychiatric care at Zuckerberg San Francisco General Hospital, on the campus where OTOP is located. Suspected psychiatric disorders discovered during screening will be referred for ongoing treatment. If the patient is at OTOP, Dr. Tompkins will provide this service. If at another opioid treatment program, the patient will be referred to a near-by San Francisco mental health treatment provider (Westside Community Service or Dore Urgent Care Center). These clinics offer urgent care, drop-in and ongoing psychiatric treatment for patients regardless of ability to pay. Ancillary, non-opioid medications, and ice packs will also be available to treat residual withdrawal symptoms or pain at end of session.

3 STUDY OBJECTIVES

We hypothesize that the chronic pain group (PAIN) will show greater delay discounting (greater impulsivity) than the group without pain (NO PAIN) in both the control and opioid withdrawal sessions; and that discounting will be greater in the withdrawal session than control session for both groups, with the greatest discounting observed in the PAIN group while in withdrawal.

We also hypothesize that across PAIN and NO PAIN groups, pain catastrophizing will independently modify the effect of precipitated opioid withdrawal on delay discounting, with higher levels of catastrophizing associated with a stronger association between withdrawal and delay discounting

3.1 Primary Objective

Determine the effect of aversive stressors on delay discounting in persons on methadone maintenance.

3.2 Secondary Objectives

Investigate the degree to which trait pain catastrophizing modifies the association between opioid withdrawal and delay discounting.

4 STUDY DESIGN

4.1 Study Overview

This is an outpatient Phase 1 clinical trial investigating the effect of naloxone precipitated withdrawal on delay discounting. Eligible participants will undergo two experimental sessions presented in random order. One session will involve the measurement of delay discounting 30 minutes after double-blind intramuscular (IM) administration of placebo (normal saline) and the other will have the exact same procedures performed after double-blind IM administration of naloxone (0.1 mg). Injections will occur 2 hours after methadone dosing (peak levels). Study sessions will last 2 hours and involve pain and opioid withdrawal measures assessed at baseline and 15-minute intervals after injections. Sessions will occur at least 48 hours apart.

This is a two-year grant proposal. The first two months will be used for study start-up, the next 20 months for study recruitment and completion of all study visits, and the last two months for data analysis and manuscript preparation. Each participant is expected to participate for 2-4 weeks, depending on scheduling of two sessions.

There are three sites on the campus of Zuckerberg San Francisco General Hospital where activities will take place. (1) Opiate Treatment Outpatient Program (OTOP). Participant recruitment, data collection and storage, and some study visits will take place at OTOP. (2) Unit 5B in Building 5. ECGs during screening and unblinded study medication preparation. (3) Ward 84 in Building 80. Some study sessions may take place at Ward 84. Johns Hopkins University's Behavioral Pharmacology Research Unit (BPRU) will be the site of data analysis. Johns Hopkins will only have access to de-identified human subject data, and so a central IRB is not needed for this study.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

Delay discounting for money will be assessed 30 minutes after study medication IM injection in both experimental sessions. Discount rates (k values) will be assessed with a computer program developed by Dr. Johnson, utilized in a variety of previous studies of delay discounting.

5.2 Secondary Efficacy Endpoints

Secondary outcome variables will include measures of pain and opioid withdrawal, i.e.

- Pain Visual Analog Scale (VAS)
- Clinical Opiate Withdrawal Scale (COWS)
- Subjective Opiate Withdrawal Scale (SOWS)
- Vital Signs
- Pupil Diameter
- VAS Ratings of Subjective Drug Effects

In addition, personality questionnaires assessing impulsivity will be collected at screening and compared across groups, including

- Barratt Impulsivity Scale-11
- Eysenck Impulsivity Questionnaire
- Sensation Seeking Scale
- Zimbardo Time Perspective Inventory

In addition, pain catastrophizing will be assessed and will be a main predictor variable in the linear regression models assessing effect modification in study Aim 2.

5.3 Safety Evaluations

- Incidence of adverse events
- Change in vital signs from baseline

6 SUBJECT SELECTION

6.1 Study Population

The participants will be adult persons (age 18-65) with opioid use disorder who are currently maintained on a stable methadone maintenance dose. Half (50) of the completers will have chronic pain (PAIN group) and half will be pain free (NO PAIN group). Otherwise, the participants will be healthy enough (as determined by medical history, physical, and EKG) for study entry. Participants will be required to abstain from illicit substances and alcohol throughout the trial.

It is estimated that approximately 200 persons will have an in-person screening to enroll 130 participants on methadone maintenance that meet all inclusion/exclusion criteria. We will need 100 completers to have the necessary power to perform our statistical analysis, 50 persons in the PAIN group and 50 persons in the NO PAIN group.

6.2 Inclusion Criteria

- Male and female adults aged 18-65
- Stable methadone dose (at least 21 days) verified by contacting participant's opioid treatment program
- Understand and speak English
- Urine toxicology screen negative for drugs of abuse and positive for methadone
- Must be without by signs of intoxication as evidenced by ability to receive full dose of methadone prior to research activities

- Presence of chronic pain (>3 months) for the PAIN group and absence of pain for the NO PAIN group

6.3 Exclusion Criteria

- Unstable psychiatric illness as assessed by the Mini International Neuropsychiatric Interview (e.g. active suicidal ideation, psychosis)
- Unstable medical illness as assessed by the study's independent medical monitor (e.g. uncontrolled hypertension, recent myocardial infarction, recent stroke, unstable angina) that may be affected by precipitated withdrawal
- Prescription opioid use besides methadone
- Acute pain process unrelated to chronic pain
- Women who are pregnant or lactating
- Known allergy to naloxone.

Patients will be allowed to re-screen if it is expected that an inclusion criterion not met or an exclusion criterion met will change prior to the end of study recruitment.

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same dose of methadone throughout participation in the trial.

7.1 Allowed Medications and Treatments

Ancillary, non-opioid medications, and ice pack will also be available to treat residual withdrawal symptoms or pain at session end.

7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

- Other opioid analgesic agents other than methadone.

8 STUDY MEDICATIONS

8.1 Method of Assigning Subjects to PAIN or NO PAIN Groups

Patients with chronic pain will be identified by self-report and confirmed by history and physical performed by Dr. Tompkins or another qualified study clinician. Pain will be assessed using the miscellaneous pain questionnaire from the National Health and Nutrition Examination Survey (NHANES; (83)), the Widespread Pain Index, and the Brief Pain Inventory. Dr. Claudia Campbell will be consulted on challenging cases to help clarify the presence or absence of chronic pain.

8.2 Blinding

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or participants. The following study procedures will be in place to ensure double-blind administration of study medications.

- Access to the randomization code will be strictly controlled.
- The volume and color of IM medication administration will be the same for naloxone and placebo
- Packaging and labeling of naloxone and placebo will be identical to maintain the blind.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

The order of sessions with exact study medications will be given to Dr. Tompkins in a sealed envelope and kept in a locked file cabinet. This envelope will be readily available for un-blinding in case of medical emergency. The envelope will be destroyed by Dr. Tompkins after participant has completed study participation.

8.3 Formulation of Naloxone and Placebo

IDS pharmacy staff will be in charge of purchasing study medications (naloxone and placebo (0.9% normal saline)) from commercial sources. The final amount of each injection will be the same, not to exceed 0.5 mL per injection. Unblinded nursing staff on Unit 5B will draw up the study medication and provide to study staff, ensuring packaging and labeling are identical.

8.4 Supply of Study Drug at the Site

IDS pharmacy will order and maintain the supply of all study medications. They will follow all applicable regulations and policies for ordering, procurement, storage, dispensing and destroying unused medication. Study medication will be prepared and provided to Dr. Tompkins' staff prior to each session by unblinded Unit 5B nursing staff.

8.4.1 Dosage/Dosage Regimen

Naloxone 0.1 mg will be given via IM injection, preferably in the Deltoid region. The total volume will not exceed 0.5 mL per injection. Naloxone is a MOR antagonist that had FDA approval to be used to reverse opioid toxicity and is routinely used in experimental studies to induced mild opioid withdrawal symptoms (Strain et al., 1995, Strain et al., 1992; Mendelson et al., 1997; Kanof et al., 1991). In addition, one pre-clinical study in female stumptailed macaques maintained on morphine showed 0.1 mg naloxone administration elicited behaviors consistent with mild opioid withdrawal (Grant et al., 1988). Normal saline will be used as placebo and will also be administered via IM injection. The total volume of placebo will be equal to naloxone injection, not to exceed 0.5 mL per injection.

8.4.2 Dispensing

The IDS pharmacy staff will dispense the medications to Unit 5B nursing staff who will then draw up study medication and label to ensure blinding. Dr. Tompkins' staff will receive study medication from Unit 5B nursing staff and then administer it in Ward 95 per protocol. If the session is cancelled or rescheduled, study medication will be returned to IDS pharmacy staff for destruction according to all applicable regulations and policies.

8.4.3 Administration Instructions

Prior to session commencing, participants must give a UDS that is positive for methadone and negative for illicit substances and other prescription opioids. In addition, the participant must not have any signs of intoxication and meet pain parameters described in the inclusion / exclusion criteria. During the COVID-19 pandemic, participants must also screen negative per hospital policy to be allowed into Ward 95 to begin study sessions. Lastly, the participant will smoke 1 cigarette 20 minutes prior to injection. Dr. Tompkins or another qualified and licensed medical clinician will administer the IM injection in the deltoid muscle of the participant. The injection will occur two hours after their daily methadone dose was given.

8.5 Study Medication Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the IDS pharmacy service.

9 STUDY PROCEDURES AND GUIDELINES

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at each session. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a subinvestigator who is a physician at Screening.

9.1.5 Vital Signs

Blood pressure, pulse and respirations will be performed after resting for 5 minutes at Screening and at beginning of each session. During sessions, blood pressure, pulse and respirations will be measured every 15 minutes up until two hours after IM injection of study medication.

9.1.6 Oximetry

Oximetry will be measured on room air with the subject at rest at Screening, at the baseline of each session and every 15 minutes during sessions up until two hours after IM injection of study medication.

9.1.7 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study (Screening) and before each study session.

9.2.2 Urine drug screen

Urine will be collected for urine drug screen at screening and on each session day. Methadone must be positive. Although current illicit drug use is not exclusionary, participants will be informed they will need to have negative urine drug screen at beginning of each session.

9.2.3 Breathalyzer

Participants will provide a breath alcohol test at screening and on each session day. Results must be 0.00 to complete screening and to begin sessions.

9.3 Pupilometer

Pupil diameter is one of the most sensitive measures of opioid withdrawal activity. Pupil diameter will be collected with a pupilometer in ambient room light (NeurOptics, Irvine, California) at baseline and every 15 minutes during sessions up until two hours after IM injection of study medication.

9.4 Impulsivity Measures

9.4.1 Delay Discounting

Delay discounting is the relative preference for smaller sooner over larger later rewards, an aspect of impulsivity. Most individuals would prefer an immediate $100 over $100 delayed by 1 year. However, when faced with the choice between receiving $95 now versus $100 in 1 year, preferences for the delayed reward may increase. By assessing such choices across multiple delays, delay discounting quantifies the devaluation of rewards over time, which allows for an index of overall discounting rate (k). Delay discounting will be measured 30 minutes after IM injection during each session.

9.4.2 Validated trait impulsivity measures.

Participants will also be assessed for trait impulsivity using four personality questionnaires assessing impulsivity or closely related constructs during screening. Scales will include the Barratt Impulsivity Scale-11 (85, 86); the Eysenck Impulsivity Questionnaire (87); the Sensation Seeking Scale (88); and the Zimbardo Time Perspective Inventory (89).

9.5 Opioid Withdrawal Measures

These measures are very familiar to the PI (Dr. Tompkins) and utilize standard tools that will be collected by trained research staff. In each session, the opioid withdrawal measures will be collected at baseline and every 15 minutes following IM injection. They include the COWS (23, 107); Subjective Opiate Withdrawal Scale (SOWS) (24), and VAS ratings of subjective drug effects (108, 109).

The COWS is an 11-item rating system that is completed by a trained observer. Total scores range from 0 to 47, and withdrawal is classified as mild (5–12), moderate (13–24), moderately severe (25–36), or severe (>36).

The SOWS is a self-report instrument that asks participants to rate their level of current opioid withdrawal on 16 symptoms using a 5-point Likert scale (Not At All to Extremely). Answers to the 16 items are summed for a total score.

There are six VASs of subjective drug effects: high, drug effect, good effects, bad effects, liking, and sick. Each scale is a 100-point line anchored at one end with “not at all,” and at the other with “extremely.” The participant positions an arrow along the line using the keypad to indicate his or her answer of how s/he is feeling at that moment.

9.6 Pain Measures

9.6.1 Pain VAS

Ratings are completed on a computer; using a mouse. The participant positions an arrow along a 100 mm line marked at either end with “none” and “worst pain imaginable.” Ratings will be collected at Screening, session baseline and every 15 minutes during sessions up until two hours after IM injection of study medication.

9.6.2 Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) is a 13-item scale that assesses important affective and cognitive aspects of pain.43 The PCS instructions asked participants to reflect on past painful experiences and to indicate the degree to which they experienced a particular thought or feeling when experiencing pain. Responses were rated on a 5-point scale from 0 (“Not at All”) to 4 (“All the Time”). Pain Catastrophizing Scale scores range from 0 to 52, with higher scores indicating heightened distress responses when exposed to aversive stimuli. The PCS will be measured in Session 1.

9.6.3 Brief Pain Inventory – Short Form

The BPI (94) is a 9 item self-report questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The patient is asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10 point scale. The BPI will be used at screening to screen for the presence or absence of chronic pain. Additionally, BPI "pain right now" VAS will be asked at beginning of each session. This score must be 0 for patients with NO PAIN or the session will be rescheduled. PAIN group persons must report similar levels of pain each session (i.e., the BPI "pain right now" score at session 2 must be +/-20% of the "pain right now" score at session 1; PAIN group persons cannot have a "pain right now" score of 0) or the session will be rescheduled.

9.6.4 Pain Assessments

Pain will be assessed using the miscellaneous pain questionnaire from the National Health and Nutrition Examination Survey (NHANES; (83)) and the Widespread Pain Index.

9.6.5 Insomnia Assessment

The Insomnia Severity Index is a brief validated instrument that measures nighttime and daytime aspects of insomnia (84). Scores 15+ indicate clinical insomnia that is at least moderate in severity. Persons found to have clinical insomnia will be referred for further evaluation and possible treatment by their primary care provider and/or their methadone maintenance medical team.

9.7 Psychiatric Assessments

The Mini International Neuropsychiatric Interview will be conducted by Dr. Tompkins during screening to rule out persons with suicidal ideation or psychosis. In addition, the following scales will also be measured at Session 1: PHQ-15 (3) which provides a measure of somatization), PHQ-9 (4) which measures depressive symptoms, and GAD-7 (5) which measures anxiety symptoms.

10 EVALUATIONS BY VISIT

10.1 Visit 1 (Screening)

1. Review the study with the subject and obtain written informed consent and HIPAA authorization
2. Assign the subject a unique screening number
3. Collect urine for urine drug screen (and pregnancy test if female)
4. Collect ROI for opioid treatment program
5. Record demographics data
6. Record medical history
7. Record drug use history
8. Record concomitant medications

9. Perform a complete physical examination
10. Perform and record vital signs
11. Perform and record oximetry
12. Perform and record EKG
13. Perform and record MINI
14. Perform and record BPI
15. Perform and record NHANES Miscellaneous Pain Questionnaire
16. Perform and record Widespread Pain Index
17. Perform and record BPI
18. Schedule subject for Visit 2 (Session 1) as appropriate.
19. Randomize subject

10.2 Visits 2-3 (Sessions 1-2)

1. Record any Adverse Experiences
2. Concomitant medications review
3. Collect Urine for UDS (and pregnancy test if female)
4. Perform and record "pain right now" VAS from BPI
5. Record time of methadone dosing (confirm by reviewing Methasoft EHR)
6. Perform and record baseline values of
    a. Vital signs
    b. Oximetry
    c. Pupilometer
    d. COWS
    e. SOWS
    f. Pain VAS
7. If smoker, allow participant to smoke 20 minutes prior to study drug administration
8. Administer IM study drug. Record on progress note.
9. For every 15 minutes until two hours after IM injection, measure
    a. Vital signs
    b. Oximetry
    c. Pupilometer
    d. COWS
    e. SOWS
    f. Pain VAS
    g. Subjective drug effect VASs

10. 30 minutes after study drug administration, perform and record delay discounting task
11. Perform and record PCS
12. Perform and record PHQ-15
13. Perform and record GAD-7
14. Perform and record PHQ-9
15. Perform and record Barratt Impulsivity Scale-11
16. Perform and record Eysenck Impulsivity Questionnaire
17. Perform and record Sensation Seeking Scale
18. Perform and record Zimbardo Time Perspective Inventory
19. Perform and record Insomnia Severity Index

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity

- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Medical Monitoring

Dr. Scott Steiger should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: 628-206-6479
Cell: 206-375-8840

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Withdrawal of Subjects

A subject may be discontinued from study treatment at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Recurrent intoxication or + UDS
- Lost to follow-up
- Positive pregnancy test (females)
- Change in methadone dose between Sessions 1 & 2
- +COVID-19 test or inability to enter Ward 95 due to screening positive for COVID-19 symptoms/recent exposure

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.2 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The PI will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the PI. A copy of the form will be filed in the site's regulatory binder.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

Completer analysis will be the data collected for all of the completers (N=100 expected).

14.2 Demographic and Baseline Characteristics

The PAIN and NO PAIN groups will be compared on all matching variables (methadone dose, cigarettes smoked per day, annual income, years of education, and age) using t-tests and chi-square tests as appropriate. If statistically significant differences are detected despite efforts to match during recruitment, matching variables will be included as covariates in subsequent analyses. It is recognized that this method is inferior to formal matching; therefore, substantial effort will be devoted to locating appropriately matched individuals. Measures obtained at 15-minute intervals during each session (pain, vital signs, opioid withdrawal, etc.) will be examined in terms of group comparability and to

confirm that naloxone precipitated withdrawal symptoms compared to placebo. All psychometric, scaled measures will be scored according to standardized algorithms and internal consistency reliability examined. Given the design of the study, unit level missing data is not anticipated. Item level missing data will be minimized through supervised administration of measures. Missing data patterns will be examined and multiple imputation (SAS PROC MI) or other strategies employed as appropriate. Using methods developed by co-I Johnson, nonlinear regression will be used to calculate individual values of k, larger k values indicate greater discounting or more impulsiveness. K values are normalized using log transformation for parametric analysis (45).

14.3 Analysis of Primary Endpoint

The primary hypotheses are that participants with chronic pain (PAIN) are more impulsive (larger k values) than participants without pain (NO PAIN) and that, within the same individual, k values will be larger in the naloxone-precipitated opioid withdrawal session compared to placebo. We will test these hypotheses using repeated measures analyses implemented in SAS PROC MIXED. The dependent variable is k (discounting). Independent variables include Group (PAIN vs. NO PAIN), a fixed, between-subjects effect and Condition (control vs. withdrawal), a repeated, within-subjects effect. The Group x Condition interaction will be examined to determine if group differences vary by condition. Planned contrasts will explore additive effects of chronic pain and withdrawal by examining whether discounting by the PAIN group in the withdrawal condition is greater than 1) discounting by the PAIN group in the control condition, or 2) discounting by the NO PAIN group in the withdrawal condition. To examine the effect of differing levels of peak aversive stimuli on discounting, we will conduct analyses using only data from the naloxone-precipitated withdrawal session that include peak COWS scores.

14.4 Analysis of Secondary Endpoints

First, general linear model analyses (SAS PROC GLM) will be conducted to independently examine the impact of Condition and Pain Catastrophizing (PCS) on discounting rate (k). Then, a single GLM analysis will be conducted that includes Condition, PCS, and the Condition–by-PCS interaction. A significant interaction will indicate effect modification. We will also examine the effect of biological sex on discounting, opioid withdrawal, pain VAS, and pain catastrophizing. Based on prior research, we expect females to have higher PCS scores. We will also explore how the type of chronic pain (musculoskeletal, neuropathic, mixed/other) will effect discounting. We will also explore associations between somatization (SCL-90), depression (PHQ-9) and anxiety (GAD-7) and discounting. ng.

Safety and tolerability data will be summarized by study medication.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by study medication and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

14.5 Interim Analysis

Researchers will look at the data from the first 10 completers. If there is no trend of differences in delay discounting between placebo and naloxone administration sessions, we would discuss with our NIDA program official and independent medical monitor (Dr. Scott Steiger) on the following two options: increasing the dose of naloxone to 0.15 mg or administering 0.1 mg naloxone at trough instead of peak methadone levels.

14.6 Sample Size and Randomization

Because the within subject effect size of discounting changes associated with naloxone precipitated withdrawal are empirically unknown, an expected effect size of f^2=.02 was assumed based on a study by Dr. Johnson (consortium PI) showing that five days of cigarette smoking abstinence in nicotine-dependent individuals decreased discounting rates (93). This effect size was selected because it came from a study conducted by a study investigator showing a within-subject change in discounting for money, similar to the delay discounting outcome in the proposed study. The effect size for between subject differences in discounting between the PAIN and NO PAIN groups is expected to be f^2=.08 for two reasons. First, the pilot data correlation between pain and discounting (rho=.25) suggests an effect size of small to medium magnitude by convention (110). Second, three previously reported effect sizes for studies comparing opioid and tobacco dependent participants to non-dependent participants (100) show larger effects sizes of approximately f^2=.4. If between subject differences in the proposed study are of this larger magnitude, then sample size based on f^2=.08 will provide more than sufficient power to detect a group difference in delay discounting rates.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug. Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials.
For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period determined by UCSF and NIH guidelines.

15.6 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be

kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

16.4 Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
5. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
6. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
7. Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects or others.
8. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
9. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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