

HPTN 058

A phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and death among opiate dependent injectors

BUP/NX TREATMENT MANUAL

Version 6.0 August 2010

Adapted from the *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction TIP 40*, U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Substance Abuse Treatment

TABLE of CONTENTS

1.0 Overview	3
1.1 Purpose of Manual	3
1.2 Relationship of Medication and Counseling	3
2.0 General Introduction to the Pharmacology of BUP/NX	3
2.1 Opioid Effects in the Brain	4
2.2 Withdrawal from Opioids	5
2.3. Safety, Adverse Reactions, and Drug Interactions	6
2.3.1 Respiratory Depression	6
2.3.3 Hepatic Effects.....	7
2.3.4 Pregnant Women and Neonates.....	7
2.3.5 Drug Interactions	8
3.0 Procedures during HPTN 058 Dosing Visits:	9
3.1 Induction Days 1-3	10
3.1.1 Procedures for Day 1	10
3.1.2 Procedures for Days 2 and 3	11
3.2 Short Term Medication Assisted Treatment Arm: Day 4 onward.....	13
3.2.1 Second Short Term Medication Assisted Treatment at Six Months	14
3.3 Long Term Medication Assisted Treatment Arm: Stabilization Day 4 through Day 21	15
3.4 Maintaining until Week 47	16
3.4.2 Missed Dosing Visits.....	17
3.4.3 Dose Tapering Week 47-52	19
4.0 Procedures for Temporarily Withholding or for Discontinuing BUP/NX.....	19
4.1 Temporarily Withholding BUP/NX Doses	19
4.2 Discontinuing Study Drug.....	20
5.0 Other Testing	20
5.1 Urine Drug Screens	20
5.2 Pregnancy Testing	20
APPENDIX A: Package Insert	21
APPENDIX B: Treatment Contract	21

1.0 Overview

In October 2002, the US Federal Drug Administration (FDA) approved the use of sublingual buprenorphine/naloxone (BUP/NX), which is marketed under the trade name Suboxone[®], for the treatment of opioid dependence. Buprenorphine is the active agent that substitutes for the abused opioid; the addition of naloxone lessens the risk of misuse by injection. This drug was selected as the pharmacological agent in the HPTN 058 trial because of its safety profile, its manageable administration schedule, and its reduced risk of diversion.

1.1 Purpose of Manual

This BUP/NX Treatment Manual addresses two areas. First, it provides an introduction to BUP/NX. Second, it specifies research procedures for the administration of BUP/NX in HPTN 058. In the introduction to the use of BUP/NX, the goal is to provide general guidance for the most effective administration of this medication in an outpatient setting for study participants. In the research area, the goal is to clearly outline procedures and practices that will be carried out at the research sites to ensure maximum consistency across study locations. This manual assumes that the clinicians involved with HPTN 058 have a basic understanding of opioid dependence and approaches to treatment; readers are also assumed to have detailed knowledge of the HPTN 058 protocol.

In addition to this manual, the clinicians will use the following documents during the course of conducting HPTN 058:

- HPTN 058 protocol, latest approved version
- Study Specific Procedures Manual (SSP), latest version
- Suboxone Package Insert (Appendix A of this manual)
- Treatment Contract (Appendix B)

The major aim of the study—for which this BUP/NX Treatment Manual has been generated—is to compare the efficacy of drug- and risk-reduction counseling plus either short-term medication assisted treatment with BUP/NX (up to 18 days) or long-term (52 weeks) maintenance with BUP/NX. Throughout this manual the term “clinician” is used, and may refer to doctors, nurses, or other staff who are qualified to administer BUP/NX. Only adequately trained physicians may **prescribe** or change the dose of BUP/NX for study participants; however, other trained staff members who meet relevant local requirements may **administer** BUP/NX to study participants.

This manual was adapted from the *TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction*, Substance Abuse and Mental Health Services Administration (www.samsha.gov).

1.2 Relationship of Medication and Counseling

Counseling and medication management begin together at randomization, with visits occurring at the same time and in the same facility as often as possible to reduce participant inconvenience and increase compliance. Clinicians and counselors should consult each other regularly about participants’ overall progress in substance abuse treatment; however, each treatment modality proceeds according to its specified procedures as stated in the protocol, in the Study Specific Procedures Manual (SSP), and in the respective treatment manuals. Clinicians and counselors will become familiar with both the counseling and BUP/NX manuals so that the treatment of participants will be coordinated.

2.0 General Introduction to the Pharmacology of BUP/NX

Detailed information about the pharmacology of BUP/NX is available in the package insert in Appendix A. The term “opioid” will be used throughout this manual as a general term to describe both opiates and opioids.

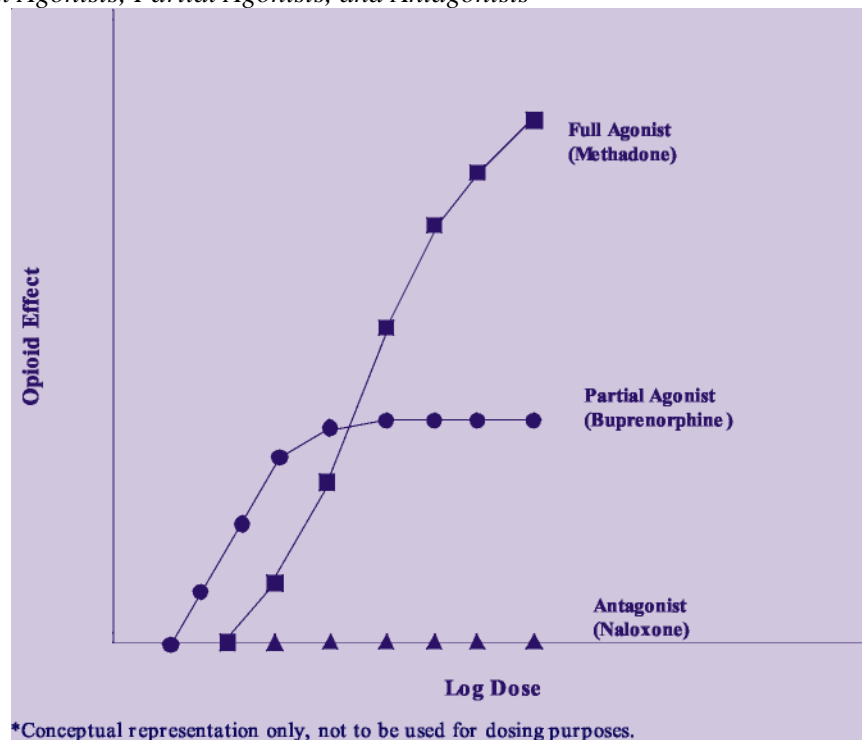
2.1 Opioid Effects in the Brain

Opioid receptors are molecules on the surfaces of brain cells to which opioids attach and exert their effects. It is through the activation of the mu receptor that opioids create their analgesic, euphoric, and addictive effects.

Morphine, heroin and methadone are *full agonists* at the opioid receptor. These agents are very effective analgesics and may also produce euphoria. As the dose of a full opioid agonist is increased, the maximal opioid effect can be achieved, resulting in respiratory depression, respiratory arrest, and death. Naloxone is an opioid *antagonist*, meaning that this drug binds with high affinity to opiate receptors, but does not activate the receptors at all (it blocks the receptors). Naloxone is sometimes administered by emergency medical personnel to reverse the effect of an overdose with a full opioid agonist.

Buprenorphine is a derivative of the morphine alkaloid thebaine, and has been used as a pain medication since the 1970’s. Buprenorphine is a *partial agonist* at the opiate receptor. This means that buprenorphine binds to opiate receptors with high affinity, but is not capable of fully activating the receptors as do *full agonists*, such as heroin or methadone. At lower doses, full and partial agonists produce similar effects (in fact at low doses, buprenorphine is actually a more potent analgesic than morphine). However, in contrast to full agonists, at higher doses, a partial agonist ceases to produce more opiate effect as the dose is further increased, a phenomenon sometimes called a “ceiling” effect. (See Figure 1) This ceiling effect means the risk of overdose is substantially lower with buprenorphine than it is with a full agonist.

Figure 1. Conceptual Representation of Opioid Effect versus Log Dose for Opioid Full Agonists, Partial Agonists, and Antagonists*



Buprenorphine has poor bioavailability when taken orally and swallowed, because of extensive first-pass hepatic metabolism. However, buprenorphine has adequate bioavailability when dissolved sublingually. Naloxone, in contrast, has very poor bioavailability irrespective of whether it is swallowed or dissolved sublingually. Thus, when dissolved sublingually a tablet of BUP/NX will produce a predominant buprenorphine effect without any interference from naloxone. However, if BUP/NX tablets are misused by crushing and dissolving the tablets and injecting the drugs under the skin or into a vein, the predominant effect will be opioid receptor antagonism by naloxone. In opioid dependent individuals misuse of BUP/NX tablets in this way is highly likely to produce intense opioid withdrawal symptoms. Hence the presence of naloxone in BUP/NX combination tablets strongly discourages misuse of the tablets by injection, and also likely reduces the street market value of the pills.

2.2 Withdrawal from Opioids

Repeated use of a mu opioid agonist results in tolerance and physical dependence. When physically dependent individuals reduce or stop opioid use, they typically develop characteristic signs and symptoms of opioid withdrawal. Withdrawal signs and symptoms include nausea, vomiting, muscle and joint aches, diarrhea, sweating, rhinorrhea, piloerection, and yawning. In an individual who is in otherwise good health, withdrawal is not life threatening. Participants with cardiovascular disease or other severe conditions will need special medical attention.

There are two types of withdrawal associated with opioid dependence: *spontaneous* withdrawal and *precipitated* withdrawal. Spontaneous withdrawal can occur when an individual who is dependent suddenly discontinues or markedly reduces opioid use. Spontaneous withdrawal usually begins 6-12 hours after the last dose of short-acting opioids, such as heroin, and peaks 36-72 hours after last use.

Precipitated withdrawal usually occurs when a physically dependent individual receives an opioid *antagonist* or *partial agonist* while under the effects of a full opioid agonist. The onset of precipitated withdrawal is much faster than spontaneous withdrawal (minutes to hours) but the symptoms are similar. Participants in HPTN 058 must present measurable signs of *spontaneous* withdrawal prior to receiving the first dose of BUP/NX in order to minimize the risk of *precipitated* withdrawal.

2.3. Safety, Adverse Reactions, and Drug Interactions

For additional instructions regarding toxicity management, dose adjustment, and safety reporting, study staff should refer to section 4 of this manual, HPTN 058 protocol section 6 and the Study Specific Procedures (SSP) Manual, section 12.

Because of buprenorphine's poor gastrointestinal bioavailability, swallowing the tablets will result in a milder effect compared with sublingual administration. The bioavailability of swallowed buprenorphine has only approximately one-fifth of the bioavailability when dissolved sublingually. Buprenorphine's "ceiling" opioid effect also adds to its safety in accidental or intentional overdose. In particular, the potential for drug-induced respiratory depression is much less of a risk with buprenorphine than it is with a full opioid agonist, like methadone. Liver function must be monitored closely in study participants, especially those with chronic viral hepatitis.

The most common side effects associated with BUP/NX are similar to those associated with opioids, e.g., nausea, muscle aches, constipation. Tolerance to most of these effects will likely develop within a few weeks of continual treatment. Clinicians in HPTN 058 will provide appropriate clinical management of these side effects, and may treat symptomatically or adjust the BUP/NX dose appropriately. It is important for clinicians to prepare participants for the possibility of some temporary discomfort during the transition process and to reassure participants that many of the side effects they feel will dissipate.

2.3.1 Respiratory Depression

Overdose of BUP/NX does not appear to cause lethal respiratory depression in noncompromised individuals. However, misuse of buprenorphine combined with other medications or illicit drugs, especially other sedative drugs or alcohol, has been associated with fatal overdoses (section 2.3.5). Some investigators have reported cases of respiratory depression induced by buprenorphine in individuals who were not physically dependent on opioids. In HPTN 058 the vast majority of doses will be supervised, greatly reducing the risk of overdose. Additionally, most overdose deaths involving buprenorphine have been associated with injection of the buprenorphine product without naloxone. The inclusion of naloxone in the BUP/NX tablets is a strong deterrent to misuse of the drug by injection in opioid-dependent individuals.

In cases of suspected overdose (e.g., somnolence, difficult to arouse), the study physician should be contacted immediately. Initial focus should be on protecting the participant's airway, monitoring breathing, pulse and blood pressure. Other drugs, alcohol, or acute medical conditions should be considered.

2.3.2 Precipitated Withdrawal

Precipitated opioid withdrawal can occur in two ways with BUP/NX. First, BUP/NX that has been intentionally misused by crushing tablets and injecting is highly likely to produce opioid withdrawal in dependent individuals because the opioid antagonist effect of naloxone predominates when injected. Participants in the study should be informed of this medication characteristic. Second, precipitated withdrawal may result if a dependent individual receives a dose of BUP/NX while under the effect of a full opioid agonist. Buprenorphine has a higher binding affinity for the opioid mu-receptors than full

agonists, like heroin. This means that buprenorphine effects are dominant when present in the system with a full agonist. Because buprenorphine is a partial agonist, it produces a sub-maximal opiate effect, regardless of the buprenorphine dose or concentration. Participants who are under the effect of a full agonist when buprenorphine is first administered can experience this decrease in opioid “effect” as withdrawal.

This type of precipitated withdrawal is generally only seen with the first dose of buprenorphine, and it is milder than the withdrawal that is precipitated by an opioid antagonist, like naloxone or naltrexone. Strategies in HPTN 058 to reduce the risk of precipitated opioid withdrawal include: 1) educating participants about the reason why they are asked to come to their randomization visits in mild to moderate withdrawal; 2) inquiring in detail about participants’ recent use of opioids and the types of opioids used; and 3) assuring mild to moderate withdrawal or greater by monitoring with the Clinical Opiate Withdrawal Scale (COWS) prior to randomization and induction. Precipitated withdrawal can be managed by reassurance, use of adjunctive medications (e.g., ibuprofen for muscle cramps, antinausea and antidiarrheal agents), and slowly proceeding with BUP/NX induction.

2.3.3 Hepatic Effects

Elevation in liver enzymes (i.e., ALT) is a concern for individuals receiving buprenorphine. Mild elevations in liver enzymes have been noted in participants with hepatitis who received long-term buprenorphine. All participants in HPTN 058 will have bilirubin and ALT testing at baseline and quarterly during the first year of enrollment. Clinicians will monitor these lab results to assess fluctuations in liver inflammation or elevations in serum bilirubin. Clinicians should also monitor participants for clinical signs of acute hepatitis – nausea, vomiting, abdominal discomfort, and jaundice. Any suspected case of hepatitis should be reported to the study physician immediately. Alternative causes of hepatitis – including alcoholic hepatitis, acute viral hepatitis, and other medications – should be considered in addition to BUP/NX. BUP/NX should be temporarily discontinued in any acute case of hepatitis involving jaundice or an elevation of the ALT > 10-times the upper limit of normal. In order to prevent the advent of severe withdrawal symptoms, participants should be tapered off of BUP/NX slowly based on the best judgment of the clinician. The Protocol Safety Review Team (PSRT) should be notified of such occurrences at 058PSRT@HPTN.org. After evaluation, treatment, and resolution of the hepatitis, BUP/NX may be reinitiated if deemed appropriate by the site PI and after consultation with the PSRT via the PSRT Query Form. . The PSRT may have suggestions for the site clinician in determining re-induction procedures, discontinuation of drug, and/or the need for repeat liver function tests.

2.3.4 Pregnant Women and Neonates

Pregnancy is an exclusion criterion for HPTN 058. Buprenorphine is a Pregnancy Category C drug. The US Food and Drug Administration (FDA) assigns a prescription drug Category C if: 1) animal reproduction studies have shown an adverse effect on the fetus; 2) there are no adequate and well-controlled studies in humans; and 3) the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. The risks of naloxone to the developing fetus are unknown. Because both mother and fetus will be dependent on the opioids used by the mother, administration of naloxone could precipitate withdrawal in both. Thus, a woman may enroll in the study only if she is unable to become pregnant or is using, or willing to use, an acceptable method of contraception for the first 52 Weeks of the study.

Buprenorphine does pass through breast milk. Women who enroll in HPTN 058 must not be breastfeeding. All women enrolled in the study will have a urine pregnancy test at screening, enrollment, randomization (if different day than enrollment) and Week 4; women enrolled in the LTMAT arm will have pregnancy tests each month during the 52

Weeks of treatment. Clinicians must review the results of the pregnancy test before recommending continuation of BUP/NX and refer to this review each month. Women who become pregnant or are found to be breastfeeding while receiving BUP/NX will be gradually withdrawn from BUP/NX and referred to appropriate perinatal care. However, even if permanently discontinued from BUP/NX, pregnant women will continue with all other study activities, including counseling and follow-up visits for HIV testing.

2.3.5 Drug Interactions

Benzodiazepines and other sedative drugs. Deaths have been reported when buprenorphine has been combined with other drugs, particularly central nervous system (CNS) depressants such as benzodiazepines. In these cases, buprenorphine tablets have typically been pulverized and then administered intravenously. Although not studied fully, it should be assumed that equal risks are associated with concurrent use of other CNS depressants, such as barbiturates and alcohol. Although polysubstance abuse or dependence should be assessed during screening, and those who are injecting other substances regularly excluded from enrollment, HPTN 058 staff should remain alert to the presence of other substance abuse throughout the course of the study. Clinicians may determine that it is not safe to continue with BUP/NX dosing if the participant is also abusing these other substances.

Medications metabolized by cytochrome P450 3A4. Buprenorphine is metabolized by the cytochrome P450 3A4 isoenzyme and may interact with other medications metabolized by the same system. Other medications that interact with this enzyme system should be used with caution in participants taking buprenorphine. Table 1 lists some of the drugs known to be metabolized by cytochrome P450 3A4.

In some cases, these drugs may either increase or decrease the buprenorphine serum concentration and exposure. CYP-450 3A4 inhibitor drugs may increase buprenorphine serum concentrations by inhibiting the metabolism of buprenorphine. Other drugs that induce the cytochrome P450 3A4 system may decrease serum concentrations of buprenorphine, potentially resulting in opioid withdrawal or decreased effectiveness. These drugs include certain antituberculosis and anticonvulsant drugs. When a participant who is receiving BUP/NX requires a drug that is a potent inhibitor or inducer of 3A4, the participant should be monitored for signs and symptoms of increased sedation or opioid withdrawal, respectively. The dose of BUP/NX should be adjusted to clinical effect. Substrates are other drugs that are metabolized by CYP-450 3A4, and may be affected by buprenorphine. Buprenorphine is a weak inhibitor of 3A4, and subsequently it is not anticipated to have clinically significant effects on 3A4 substrates.

Table 1. Sample of drugs that may affect BUP serum concentrations via CYP 3A4 system

<u>Inhibitors (↑ BUP levels)</u>	<u>Inducers (↓ BUP levels)</u>
<ul style="list-style-type: none">• Erythromycin• Clarithromycin• Fluconazole• Ketoconazole• Omeprazole• Grapefruit/Pomelo juice• Paroxetine• Verapamil	<ul style="list-style-type: none">• Rifampin• Carbamazepine• Phenytoin• Phenobarbital• Nevirapine• Efavirenz

3.0 Procedures during HPTN 058 Dosing Visits:

All HPTN 058 staff involved with study visits are expected to use the **Visit Checklists** to guide each encounter with participants. Template Visit Checklists are in Section 6 of the SSP Manual. Each site is expected to modify the visit checklists, within the constraints of the protocol, in order to meet their site needs.

Ideally, participants will have one clinician throughout the treatment phase who will monitor dosing, clinical status and medication effects. The clinician should attempt to develop an accepting and supportive relationship with the participant and to convey optimism regarding the outcome of treatment. The clinician should clearly link this expectation of improvement with attendance at all counseling sessions and adherence to the drug regimen to which the participant has been assigned.

Except for the early visits, which will last several hours so that the physician can adjust dosing, most medication visits will last about 15 minutes. All visit procedures should be conducted in a private setting where conversations cannot be overheard by other participants or staff. Visits should be scheduled so that waiting is minimal and, when possible, combined with other study activities like counseling sessions to reduce burden on study participants.

NOTES:

- Only physicians may prescribe, change, or discontinue dosing. However, other qualified staff may administer the drug to the participant.
- If the participant is receiving both counseling and medication sessions the same day, the preferred treatment order is counseling first followed by medication.
- The study coordinator or other specified staff may review withdrawal symptoms, complete the DataFax Concomitant Medication Log (CM-1), and make next appointment prior to the participant meeting with the clinician.
- Procedures for grading and reporting adverse events are presented in the DAIDS Manual for Expedited Reporting of Adverse Events to DAIDS (see Appendix D in the SSP).

3.1 Induction Days 1-3

Detailed checklists for each visit are included in Section 6 of the SSP.

By the time participants are ready to begin induction they will have had the study explained in detail to them, participant comprehension will have been confirmed, the participant's questions will have been answered, the benefits and risks of BUP/NX will have been discussed and the participant will have consented for the study. Prior to the randomization visit, the study physician will have confirmed eligibility for enrollment. Participants will be asked to abstain from opioid use after 6PM of the night prior to induction. Participants who abuse long-acting opioids (e.g., methadone) should be asked to abstain from these drugs for at least 24 hours. A longer period of opioid abstinence at induction reduces the risk of precipitated opioid withdrawal.

The participant must exhibit signs and symptoms of opioid withdrawal (e.g., sweating, lacrimation, goose flesh, rapid pulse) before the first dose is administered. Withdrawal symptoms will be measured by the Clinical Opiate Withdrawal Scale (COWS, which must be 8 or higher to begin as noted below). Participants who are not in active withdrawal will wait until withdrawal symptoms appear before being randomized. Participants who report that they have recently used opioids (e.g., the morning of induction) should generally be re-scheduled for induction on another day. In such a situation, staff should re-explain the need to abstain from opioids prior to BUP/NX induction.

Regardless of treatment arm assignment, the first three days' dosing procedures (Induction) are the same for all participants.

3.1.1 Procedures for Day 1

The initial medication visit will last approximately 4 to 6 hours, and will occur on the same day as randomization. Prior to beginning the induction portion of this visit, the participant should have met with the clinician or other assigned study staff to confirm that the participant has signed the enrollment consent, review the laboratory findings, and had a negative pregnancy test (if female).

The participant should only be inducted when in spontaneous withdrawal so as to avoid a precipitated withdrawal. The clinician will ask the participant the last time they used opioids, other drugs, and alcohol. Regardless of the stated time of last use of drugs, the participant should be in mild to moderate opioid withdrawal, as gauged by the COWS, prior to receiving the first dose of BUP/NX. Using the COWS, the clinician will assess each of the 11 items, assigning a value for the item at that time.

If the COWS score is less than 8, randomization/dosing should be postponed and the COWS score rechecked in one hour. If the COWS score is 8 or higher, the study staff may proceed with randomization. Designated staff will open the next sequential randomization envelope with a witness present. Inside the envelope will be a treatment assignment, either "substitution/Long term medication assisted treatment (LTMAT)" or "detoxification/short term medication assisted treatment (STMAT)." The staff will follow randomization procedures as described in the SSP, Sections 4.6 and Section 6.

The study staff should briefly explain the procedures for the particular arm of treatment to which the participant has been assigned (e.g., if in STMAT arm, explain that BUP/NX will be short-term, and that counseling will continue for a year) and answer any questions she/he may have. The participant should be given a schedule of follow up visits so she/he can plan ahead for coming to the clinic. The staff should expect and plan for the need to repeat all of this information later during this visit and subsequent visits.

The following points are relevant to BUP/NX induction Day 1.

- The participant may take a sip of water to wet his/her mouth prior to dissolving

the BUP/NX tablet(s) under the tongue, but not after the tablets have been placed in his/her mouth. Site staff should be sure that the participant has swallowed the water prior to placing tablets under the tongue, to ensure that the tablets are not inadvertently swallowed.

- Some participants that smoke within 20 minutes of dosing have a harder time dissolving the tablets. It is recommended that participants not smoke within this timeframe.
- The study staff should verify that the BUP/NX tablets are placed correctly under the participant's tongue, and instruct the participant not to chew or swallow until the pills are completely dissolved.
- The study staff should observe the participant until tablets are dissolved. If in the very rare occurrence a participant swallows the dose, the dose may be re-administered one time only.
- The participant will remain under observation for at least one hour after the first dose when the COWS will be repeated and a second dose of BUP/NX may be administered - See Table 2 below for dosing guidelines. Note that the clock should begin when the tablets are completely dissolved; however, for those participants that do not easily dissolve the tablets, the clock may begin when the tablets are ½ dissolved.
- The vast majority of participants will require 8 mg of BUP/NX on induction Day 1.
- Although the protocol does not specify a maximum BUP/NX dose for Day 1, in practice, the maximum Day 1 dose should be 8 mg, unless there are extraordinary circumstances (e.g., continued severe opioid withdrawal symptoms more than 2 hours after the second BUP/NX dose) that mitigate for more than 8 mg on Day 1 (see Table 2).
- If the participant is dependent on a long-acting opioid (e.g., methadone), it is appropriate to give 2 mg BUP/NX as first dose and observe for 1 hour. If this is well tolerated, a second dose of 2 mg may be given, followed by a dose of 4 mg after another hour.
- Participants should be reassured that they won't feel the peak effect of BUP/NX for several hours.
- If the first dose of BUP/NX makes a participant feel worse, it is possible that the medication is causing precipitated opioid withdrawal (see Section 3.1.2 below).

At the conclusion of the visit, the study staff should emphasize to the participant that other drugs such as alcohol and sleeping pills should not be used unless prescribed. Heroin, methadone, and other opioids should also not be used in order to avoid the possibility of precipitated withdrawal when BUP/NX is given on the second day. Even if 8 mg of BUP/NX is taken on day one, there are sufficient opioid receptors available for other exogenous opioids to bind to. Thus, if heroin or other opioids are taken within 8 hours of the second day BUP/NX dose, it is possible to precipitate withdrawal. Participants should be reminded not to drive a car or motorbike or operate machinery until they are sure of how BUP/NX will affect them.

3.1.2 Management of Potential Precipitated Opioid Withdrawal

- Consider precipitated withdrawal if a participant's withdrawal symptoms intensify substantially within 20 to 40 minutes after first dose of BUP/NX.
- The major risk factors for precipitated withdrawal are 1) recent use of opioids, 2) regular use of long-acting opioids (e.g., methadone), 3) high opioid tolerance and heavy use, and 4) a high first dose of BUP/NX (for this reason, it is recommended to start with an initial BUP/NX dose of only 2 mg if a subject regularly uses long-acting opioids (e.g., methadone).

- Precipitated withdrawal is uncommon when inducing subjects who are dependent on short-acting opioids (e.g., heroin).
- Reassure subject that symptoms will pass.
- Symptomatic treatment may be given – NSAIDS for aches, anti-nausea medications, judicious use of benzodiazepines for marked agitation.
- May proceed with induction after 1-2 hours if subject is feeling better. In this case, give 2 mg BUP/NX, observe for another hour and give another 2 mg of BUP/NX if indicated.

3.1.3 Procedures for Days 2 and 3

On Day 2 repeat the COWS. If the COWS ≥ 2 or if the participant reports withdrawal symptoms overnight (including use of opioids or a strong urge to use them), a dose of BUP/NX equal to the total Day 1 dose plus 4 mg should be administered. A repeat dose of 4 mg can be administered after 2 hours. It is anticipated that most participants will receive a total BUP/NX dose of 16 mg on Day 2. However, withdrawal symptoms in some participants may be well controlled with 8 mg or 12 mg. The maximum BUP/NX dose that can be used on Day 2 is 16 mg. The BUP/NX dose should not be administered within 8 hours of reported use of heroin or other opioids or 24 hours of methadone to avoid the possibility of precipitated withdrawal. This is less of a risk if the participant has taken 12 or more mg BUP/NX the prior day because there are not that many receptors available for the heroin to occupy.

On Day 3 of induction, the dosing should equal the Day 2 total dose or the Day 2 total dose plus 4 mg if necessary. Extra doses may also be administered on Day 3 (up to the 32 mg maximum) to control persistent withdrawal symptoms.

As with any pharmacotherapy, the goal of BUP/NX treatment is to use the *minimum effective* dose. The immediate goal of BUP/NX therapy is to alleviate withdrawal symptoms, with longer-term goals of reducing drug craving, and reducing or eliminating use of illicit opioids. It is important to recognize that drug using behavior has a major psychologic component that takes much longer to address than alleviating withdrawal symptoms. Ongoing drug use and relapses will be common, but should trend downward with continued treatment and counseling.

Table 2 below provides guidance for Days 1-3. It is expected that clinicians will closely adhere to the guidelines for the first 10-15 enrollees; however, these are guidelines, and, as such, clinicians may use their own clinical judgment to gauge the appropriate dosing levels for induction as long as protocol specified dosing ranges are adhered to.

Table 2. Induction Guidelines

Day 1	Day 2	Day 3
<p>If COWS = 0-7, no BUP/NX, re-administer COWS in 1 hour</p> <p>If COWS persists to be < 8, clinician may re-schedule the participant for the next day.</p> <p>If COWS ≥ 8, START WITH BUP/NX 4 mg</p> <p>Repeat COWS <u>1 hour</u> following completion of first dose</p> <p>If COWS = 0 or if participant drowsy, Day 1 dose complete (at a total of 4 mg)</p> <p>If COWS ≥ 1*, give an additional BUP/NX 4 mg (totaling 8 mg – therefore, Day 1 Induction Complete (unless continued severe opioid withdrawal symptoms more than 2 hours after the second BUP/NX dose in which case clinicians may decide to give an additional 4 mg dose)</p>	<p>If COWS < 2* and no withdrawal symptoms reported overnight, give BUP/NX at total amount received over Day 1 (which was up to 8 mg); Day 2 dose complete, observe 30 minutes</p> <p>If COWS ≥ 2* or withdrawal symptoms reported overnight, give Day 1 total BUP/NX <u>plus</u> 4 mg</p> <p>Repeat COWS <u>1-2 hours</u> following completion of first dose</p> <p>If COWS < 2* or if participant drowsy, Day 2 dose complete</p> <p>If COWS ≥ 2*, give BUP/NX 4 mg (up to a total of 16 mg for Day 2)</p>	<p>If COWS < 3* and no withdrawal symptoms reported overnight, give BUP/NX at total amount received over Day 2 (up to 16 mg); Day 3 dose complete, observe 30 minutes</p> <p>If COWS ≥ 3* or withdrawal symptoms reported overnight, give Day 2 total BUP/NX <u>plus</u> 4 mg</p> <p>Repeat COWS <u>1-2 hours</u> following first dose</p> <p>Additional dose(s), in 4 mg increments, should be considered if the COWS remains ≥ 4*</p> <p>Additional doses should be separated from one another by ≥ 1 hour</p> <p>The maximum dose for Day 3 is 32 mg.</p>

* These COWS scores are meant as guidelines; use clinical judgment. For example, consider how much the COWS score has changed from the subject’s initial COWS on Day 1, and if COWS points are based on objective findings or solely on subjective reports.

3.2 Short Term Medication Assisted Treatment Arm: Day 4 onward

Beginning on Day 4, those who are in the STMAT Arm will have their dose reduced by approximately 2 mg per day until they reach 0 mg. The daily dose changes are flexible during short term medication assisted treatment; in some cases it may be appropriate to hold a participant at a specific dose for more than one day or even to increase the dose slightly to ease withdrawal symptoms. However, the short term medication assisted treatment must be concluded by Day 19. During this transition time, the clinician may use other medications to treat symptoms that emerge and may refer to other community resources, such as self-help groups or other treatment programs to complement BDRC counseling sessions. The goal is to provide a supportive and sympathetic environment conducive to sustaining abstinence from injecting opioids and retention in the study. The table below gives an example of the dose tapering that will occur in a participant who has received a total of 16 mg on Day 3.

Table 3. Sample Dose Tapering in STMAT Arm

Day of Study	Day of Week	Dosage (mg) of BUP/NX (Expressed as Buprenorphine Component)
1-3	M	8
	Tu	16
	W	16
4-7	Th	14
	F	12
	S	18 if dose is covering two days 10 if dose is covering one day only
	Su	0 if dose on Saturday covered two days 8 mg if dosed on Sat for one day.
8-12	M	6
	Tu	4
	W	2
	Th	0

3.2.1 Second Short Term Medication Assisted Treatment at Week 26

Those in the STMAT arm may be offered a second opportunity for short term medication assisted treatment at the six-month follow-up if they are still injecting opioids. The participant must meet the following criteria:

- Meets Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for opioid dependence, as determined by study clinician
- Positive urine test for opioids
- Injected opioids at least 12 times in the last 28 days
- NOT currently or recently (within the past 12 weeks) received clinician-guided treatment for opioid dependence with methadone, LAAM, , naltrexone, or nalmefene, according to self-report
- NOT currently enrolled in another HIV prevention or drug use intervention study
- NO known clinically-diagnosed allergy to buprenorphine or naloxone, according to self-report
- DOES NOT meet the DSM-IV criteria for dependence on alcohol or benzodiazepines; requiring immediate medical attention for dependence on or other substances (except tobacco) as judged by the study clinician
- NOT currently injecting substances other than opioids more than twice in the last 28 days, according to self report
- NOT Pregnant or lactating
- NO acute or chronic renal failure as judged by study clinician
- ALT NOT greater than three times the upper limit of normal value
- Hemoglobin NOT less than 8 g/dL for men, less than 7 g/dL for women
- Platelet count NOT less than 50,000/mm³
- Total bilirubin NOT greater than 2.5 times the upper limit of normal
- Psychological disturbance or cognitive impairment interfering with the participant’s ability to comply with the study visit schedule and procedures, as judged by the local study clinician

- Other medical or psychiatric condition that, in the opinion of the investigator, would make participation in the study unsafe or otherwise interfere with the study objectives or interpretation

During the Week 26 follow-up visit, the interviewers and counselors will have indication that a participant may be eligible for second short term medication assisted treatment. For example, if the urine drug test is positive for opioids and the Risk Assessment indicates current injection behavior, the staff should inquire if the participant is interested in a second short term medication assisted treatment if they are eligible. Staff will follow the procedures in the Follow-Up Visit Checklist for Week 26 for those participants who are willing and potentially eligible for a second short term medication assisted treatment. As with screening and enrollment, the exact reason for ineligibility for a second short term medication assisted treatment should not be revealed to the participant.

Participants will have completed the Week 26 follow-up assessment visit including a DSM-IV diagnosis and targeted physical exam, and the clinician will review the lab results and other source documents before determining eligibility for second short term medication assisted treatment. If participant meets criteria for second short term medication assisted treatment and has indicated willingness, site staff will contact the participant and arrange the induction visit. Induction and dose tapering procedures at Week 26 will be the same as at enrollment. Women who undergo a second short term medication assisted treatment at Week 26 will have a pregnancy test before beginning the short term medication assisted treatment and approximately 4 weeks later and will be counseled on methods of birth control while using BUP/NX.

3.3 Long Term Medication Assisted Treatment Arm: Stabilization Day 4 through Day 21

From Day 4, the participants in the LTMAT arm will continue to receive a daily dose of BUP/NX up to Day 21. Dose adjustments are commonly needed during the first three weeks. Most participants will stabilize on daily doses of 16-24 mg; some, however, may require up to 32 mg daily. During the stabilization phase, the BUP/NX dose should not be increased more than 2 mg/day. In some cases, the daily dose of BUP/NX may be decreased if a participant reports feeling sedated or sluggish while taking the medication.

Once the participant has received a stable dose for five days, and has adjusted well, the participant will switch to three times per week dosing. Because buprenorphine is a partial agonist, maximum effects are below those expected for a full agonist. Thus, increases in dosing pose a minimal risk of overdose and are usually well-tolerated by participants. The transition from daily dosing to three times per week dosing is possible with an abrupt transition that should begin on a Monday for a Monday/Wednesday/Friday schedule. For example, a participant who has stabilized on 12 mg/day would have had 12 mg on Sunday (or 24 mg on Saturday if clinic is closed on Sunday), then

- receive 24 mg on Monday (double the stable daily dose),
- skip Tuesday,
- receive 24 mg on Wednesday,
- skip Thursday,
- receive 36 mg on Friday (3 times the daily dose) , and then
- resume dosing the following week on Monday/Wednesday/Friday.

Alternatively a Tuesday/Thursday/Saturday schedule may be used for three-times weekly dosing.

Participants should be monitored closely during the first week of three-times weekly dosing to observe for excessive opioid effects. The highest three-times weekly dosing schedule that may be used is 32/32/48 mg, which corresponds to a daily dose of 16 mg. Participants who have been stabilized on a daily dose of 16 mg or higher should be converted to the three times per week schedule of 32/32/48 mg. In unusual cases, participants who have required high daily doses of BUP/NX for stabilization may experience unacceptable withdrawal symptoms on the maximum three times per week schedule of 32/32/48 mg. In these cases, participants may remain on daily dosing or an alternative dosing schedule. For example, four-times weekly Monday/Wednesday/Friday/Saturday dosing eliminates a 72-hour period between doses, when participants are most likely to begin experiencing withdrawal symptoms.

3.4 Maintaining until Week 47

In all phases of HPTN 058, adjusting BUP/NX doses depends on assessment of withdrawal symptoms, continued craving for and use of illicit opioids, and side effects of BUP/NX. If there is persistent opioid craving or use, clinicians should consider increasing the dose of BUP/NX during the maintenance phase. Like other opioids, BUP/NX produces opioid-like side effects such as constipation or muscle aches. Mild side effects can be treated with other treatments like aspirin (muscle aches), stool softeners and mild laxatives (constipation).

Liver function tests (ALT and bilirubin) are done quarterly for all participants during the first 52 weeks (and more frequently for participants enrolled during the safety phase). Pharmacotherapy with BUP/NX is not contraindicated on the basis of mildly elevated liver enzymes, but should be monitored closely. Any suspected case of hepatitis should be reported to the study physician immediately. Alternative causes of hepatitis – including alcoholic hepatitis, acute viral hepatitis, and other medications – should be considered in addition to BUP/NX. BUP/NX should be discontinued in any case of hepatitis involving jaundice or an elevation of the ALT > 10-times the upper limit of normal. Halting BUP/NX should usually be done by tapering the participant slowly off of the medication, based on the judgment of the clinician. The PSRT should be notified immediately at **058PSRT@HPTN.org**. After evaluation, treatment, and resolution of the hepatitis, BUP/NX may be reinitiated if deemed appropriate by the site PI and consultation with the PSRT via the PSRT Query Form. In such situations the participant may need to be re-induced. Clinicians should discuss with all participants the risks associated with continued alcohol and drug abuse while taking BUP/NX.

Barring any serious safety concerns that indicate withholding or terminating BUP/NX doses (see section 4.4 of protocol), participants will continue to receive the regularly scheduled doses until Week 47. The table below illustrates what a typical dosing visit during the maintenance phase entails.

Table 4: Typical Medication Visit Following Stabilization

Timing	Topic	Form
Beginning	Welcome and check-in, confirm identity	
	Review previous Dosing Log	Dosing Log
Middle	Review monthly urine tests if scheduled (If pregnant or benzodiazepines use indicated, determine if dose adjustment needed.)	Urine Test Results
	Review any new lab results if available	Lab results
	Administer dose, observe until tablets are dissolved	Dosing Log
End	Remind about risks of using other drugs, alcohol, and of driving or using any machinery (if early in treatment)	Chart note
	Appointment for next visit	

3.4.1 Treatment Contracts

Drug dependent individuals often display disordered or manipulative behaviors. In general, it is more effective to focus on changing maladaptive behaviors directly than to search for underlying causes. Sites may decide to use treatment contracts with participants (Appendix B). A treatment contract establishes the ground rules for expected behavior at the BUP/NX dosing center and protects staff as well as other participants in the program.

3.4.2 Missed Dosing Visits

In this protocol participants are asked to attend a large number of appointments (particularly in the LTMAT arm). Sporadic missed visits will occur commonly and prolonged periods of missed visits may occur for a variety of reasons (e.g., incarceration, travel). Staff should set clear and reasonable boundaries of what is allowable for missed or late visits based on the requirements of the facility and staff. Table 5 presents guidelines for how different scenarios of missed dosing visits may be addressed. Participants who miss a dosing visit should make up that dose as soon as possible if it presents no undue burden to the staff. For example, a participant on a Tuesday, Thursday, Saturday dosing schedule who misses a regularly scheduled visit on Tuesday, could come in on Wednesday to receive half of his/her regular dose, then return again to his/her regular schedule for Thursday and Saturday. If a participant in either arm misses 1-3 consecutive dosing visits, then a regular BUP/NX dose can be given at the next scheduled dosing visit.

If a participant in the STMAT arm misses more than 3 consecutive doses of BUP/NX, short term medication assisted treatment should be considered complete.

When a participant in the LTMAT arm misses 1 or 2 doses of BUP/NX (less than 3 calendar days of dosing) there is some risk for precipitated withdrawal when BUP/NX is restarted if the participant resumes using opioids since discontinuing treatment. Investigators should use caution. When a participant in the LTMAT arm misses more than 2 consecutive doses (more than 3 consecutive calendar days) the following considerations may apply:

- Participants may be at risk for precipitated withdrawal when BUP/NX is restarted if they have resumed using opioids since discontinuing treatment.
- Participants who miss between 4 to 14 calendar days of dosing (typically approximately from 2 to 7 consecutive doses) may be restarted on their prior dose of BUP/NX. However, at least 8 to 10 hours should have elapsed since their last use of opioids to minimize the risk of precipitated withdrawal. Additionally, an abbreviated re-induction may be used. For example, a participant might be given 4 mg of BUP/NX and monitored for 1-2 hours. If tolerated with no symptoms of precipitated withdrawal, the remainder of the participant's regular dose may be given. This approach is appropriate for participants who are on a thrice weekly dosing schedule. Because a high first dose of BUP/NX is a risk factor for precipitated withdrawal (i.e., the higher doses used with thrice weekly dosing), a lower dose followed by the larger remaining dose is preferred.
- Participants who miss more than 14 calendar days (typically approximately 6 or 7 doses) of BUP/NX should undergo a formal re-induction to minimize the risk of precipitated withdrawal and because their BUP/NX dosing requirements may have changed. During this formal re-induction,

Investigators are encouraged to monitor the COWS scores prior to the initial dose, but this does not have to be 8 as in the initial induction.

- Sites may consult the PSRT with any questions that arise about restarting BUP/NX after missed doses and about restarting BUP/NX in any subject in the LTMAT arm who misses more the 14 consecutive calendar days (typically approximately 6 or 7 doses).
- It may be appropriate to refuse to restart BUP/NX in participants who have multiple episodes of treatment non-adherence (has required re-induction more than three times) and do not seem to be engaging in the treatment. Such cases should be discussed with the PSRT.
- Re-inductions should not be offered to participants who are 46 weeks or more beyond randomization, because dose tapering would typically begin at this time.

Participants who discontinue BUP/NX or counseling treatment prior to the scheduled end date, regardless of study arm or reason, will be asked to remain in the study and complete all weekly and monthly counseling and follow-up visits as originally scheduled unless otherwise specified.

Table 5. Guidance on Handling Missed Visits

Arm	Phase	Situation	Response
STMAT or LTMAT	Induction	Misses 1 or 2 days starting during induction	<ul style="list-style-type: none"> ▪ Start with total dose given on last dosing day ▪ May give additional dose(s) to control withdrawal symptoms as described in induction protocol
STMAT	Dose tapering phase	Misses 1 or 2 consecutive days of dosing	<ul style="list-style-type: none"> ▪ Give the same dose or a lower dose than that received on the last dosing day. ▪ Consider that the dose taper has to be complete by Day 18
STMAT	Induction or tapering	Misses ≥ 3 consecutive calendar days of dosing (or missed 2 consecutive doses)	<ul style="list-style-type: none"> ▪ Short term medication assisted treatment is complete ▪ Counseling and other visits continued
LTMAT	Post-induction	Misses ≤ 3 consecutive calendar days of dosing	<ul style="list-style-type: none"> ▪ Administer the regularly scheduled dose at next dosing visit
LTMAT	Post-induction	Misses >3 consecutive calendar days of dosing up to 14 consecutive calendar days	<ul style="list-style-type: none"> ▪ May administer regular dose if risk of precipitated withdrawal felt to be low ▪ Assure that 8-10 hours have passed since last use of opioid drugs ▪ Consider abbreviated re-induction if longer time since last BUP/NX dose, subject used opioids during treatment gap, and subject on thrice weekly dosing
LTMAT	Post-induction	Misses >14 calendar days of dosing (typically approximately 6 or 7 doses)	<ul style="list-style-type: none"> ▪ Formal re-induction using induction protocol ▪ Consult PSRT prior to restart only if this participant has had multiple occurrences of treatment non-adherence (has required re-induction prior to the fourth re-induction) ▪ Re-induction should not be offered if subject is 46 weeks or more beyond randomization

3.4.3 Dose Tapering Week 47-52

Study participants in the LTMAT arm will undergo dose tapering for approximately six weeks at the end of the treatment phase (Weeks 47-52). As with dose induction, the visit schedule and dosage during dose tapering will vary from participant to participant. As a general rule, doses should be reduced *slowly each week* until 0 mg dose is reached. For example, an individual maintained on a three-times-weekly dosage of 24/24/36 mg given on M/W/F could have his/her dosage decreased over six weeks according to the schedule in the following table:

Table 6. Example of Dose Tapering in LTMAT Arm

Week of Study	Day of Week	Dosage (mg) of BUP/NX (Expressed as Buprenorphine Component)
47	M	24 (12 mg/day)
	W	20 (10 mg/day)
	F	30 (10 mg/day)
48	M	18 (9 mg/day)
	W	16 (8 mg/day)
	F	24 (8 mg/day)
49	M	14 (7 mg/day)
	W	12 (6 mg/day)
	F	18 (6 mg/day)
50	M	10 (5 mg/day)
	W	8 (4 mg/day)
	F	12 (4 mg/day)
51	M	6 (3 mg/day)
	W	4 (2 mg/day)
	F	6 (2 mg/day)
52	M	2 (1 mg/day)
	W	2 (1 mg/day)
	F	0

4.0 Procedures for Temporarily Withholding or for Discontinuing BUP/NX

4.1 Temporarily Withholding BUP/NX Doses

The clinician may decide to withhold BUP/NX dosing for several reasons. For example, it is appropriate to temporarily withhold BUP/NX from a participant who comes to the clinic obviously intoxicated with drugs (particularly CNS depressants such as benzodiazepines) or alcohol. A second reason to withhold dosing is if a participant develops an acute injury or medical condition that requires opioid medications for pain control (e.g., broken arm). If this occurs, the participant can be re-induced to BUP/NX after the need for opioid medication has resolved. If a condition can be adequately managed with non-opioid medications (e.g., non-steroidal anti-inflammatory drugs) it may not be necessary to hold BUP/NX dosing. If a

participant is incarcerated or otherwise unavailable, dosing will also be withheld. The PSRT must be notified of any Investigator initiated study drug discontinuations at 058PSRT@HPTN.org.

4.2 Discontinuing Study Drug

In rare situations it may be necessary to discontinue BUP/NX in a participant. This topic is more relevant to participants who are in the LTMAT arm. The PSRT must be notified of any Investigator initiated study drug discontinuations at 058PSRT@HPTN.org. Situations in which BUP/NX discontinuation is appropriate include, 1) a serious medical event (e.g., allergic reaction or hepatic toxicity) that is believed to be caused by BUP/NX, 2) a female participant becomes pregnant (in this situation an attempt should be made to transfer the participant to methadone treatment), or 3) a participant displays unacceptable or threatening behavior. Behavior that is genuinely threatening to staff or other participants damages the therapeutic environment and should not be tolerated (see section 3.4.1). Additionally, using or selling drugs on the premises of the treatment center should not be permitted.

Continued drug or alcohol use or relapses in use will be common in study subjects. Most individuals with opioid dependence have abused substances for many years, and these behaviors are difficult to change. The general approach to ongoing substance use should be engagement and counseling. In the vast majority of situations, a participant's safety will be greater if he or she continues to be engaged in treatment than if BUP/NX treatment is discontinued. In any situation where study drug is to be discontinued an attempt should be made to taper BUP/NX dosing rather than halting dosing all together in order to prevent withdrawal symptoms.

Note: Site staff are always encouraged to consult with the PSRT if any questions remain.

5.0 Other Testing

5.1 Urine Drug Screens

Urine drug screens are conducted monthly on all participants; these tests will screen for methadone, benzodiazepines, methamphetamine, and opiates. Although not required by the protocol, more frequent urine drug screens are appropriate for monitoring participants who are receiving BUP/NX LTMAT therapy. Typically urine tests will be done at the same visit when counseling sessions are held. Counselors will review the test results with each participant during the following session; however, clinicians should also review these tests when they are available. While there is no "penalty" for continuing to use illicit drugs during the study, there are safety concerns if the participant is using other drugs, especially benzodiazepines and CNS depressants. Clinicians should evaluate whether it is safe to continue dosing participants who are using other illicit drugs based on their clinical evaluation and document their decision in chart notes.

5.2 Pregnancy Testing

All women will have a pregnancy test at screening, enrollment, randomization (if different day than enrollment) and at Week 4. All women randomized to the substitution arm should be counseled on using effective birth control while taking BUP/NX. Women in the LTMAT arm will have monthly pregnancy tests and women who undergo a second short term medication assisted treatment at six months will have a pregnancy test before beginning the short term medication assisted treatment as well as approximately 4 weeks later. If a pregnancy test is positive, the woman will be gradually tapered off BUP/NX by reducing the dose by 2 mg/day until 0 mg is reached. The site clinician will consult with the PSRT regarding appropriate referrals and follow-up.

APPENDIX A: Package Insert

APPENDIX B: Treatment Contract

Sample Treatment Agreement/Contract

As a participant in the buprenorphine protocol for treatment of opioid abuse and dependence, I freely and voluntarily agree to accept this treatment agreement/contract, as follows:

I agree to keep, and be on time to, all my scheduled appointments with the doctor and his/her assistant.

I agree to conduct myself in a courteous manner in the physician's office.

I agree not to arrive at the office intoxicated or under the influence of drugs. If I do, the doctor will not see me, and I will not be given any medication until my next scheduled appointment.

I agree not to sell, share, or give any of my medication to another individual. I understand that such mishandling of my medication is a serious violation of this agreement and would result in my treatment being terminated without recourse for appeal.

I agree not to deal, steal, or conduct any other illegal or disruptive activities in the doctor's office.

I agree that my medication (or prescriptions) can be given to me only at my regular office visits. Any missed office visits will result in my not being able to get medication until the next scheduled visit.

I agree that the medication I receive is my responsibility and that I will keep it in a safe, secure place. I agree that lost medication will not be replaced regardless of the reasons for such loss.

I agree not to obtain medications from any physicians, pharmacies, or other sources without informing my treating physician. I understand that mixing buprenorphine with other medications, especially benzodiazepines such as valium and other drugs of abuse, can be dangerous. I also understand that a number of deaths have been reported among individuals mixing buprenorphine with benzodiazepines.

I agree to take my medication as the doctor has instructed and not to alter the way I take my medication without first consulting the doctor.

I understand that medication alone is not sufficient treatment for my disease, and I agree to participate in the patient education and relapse prevention programs, as provided, to assist me in my treatment.

Printed Name

Signature

Date

From: Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series40.