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NIDA Clinical Trials Network CTN-0051, Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment (X:BOT): Study Design and Rationale

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Abstract

Introduction—For opioid-dependent patients in the US and elsewhere, detoxification and counseling-only aftercare are treatment mainstays. Long-term abstinence is rarely achieved; many patients relapse and overdose after detoxification. Methadone, buprenorphine-naloxone (BUP-NX) and extended-release naltrexone (XR-NTX) can prevent opioid relapse but are underutilized. This study is intended to develop an evidence-base to help patients and providers make informed choices and to foster wider adoption of relapse-prevention pharmacotherapies.

Methods—The National Institute on Drug Abuse's Clinical Trials Network (CTN) study CTN-0051, X:BOT, is a comparative effectiveness study of treatment for 24 weeks with XR-NTX, an opioid antagonist, versus BUP-NX, a high affinity partial opioid agonist, for opioid dependent

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patients initiating treatment at 8 short-term residential (detoxification) units and continuing care as outpatients. Up to 600 participants are randomized (1:1) to XR-NTX or BUP-NX.

Results—The primary outcome is time to opioid relapse (i.e., loss of persistent abstinence) across the 24-week treatment phase. Differences between arms in the distribution of time-to-relapse will be compared (construction of the asymptotic 95% CI for the hazard ratio of the difference between arms). Secondary outcomes include proportions retained in treatment, rates of opioid abstinence, adverse events, cigarette, alcohol, and other drug use, and HIV risk behaviors; opioid cravings, quality of life, cognitive function, genetic moderators, and cost effectiveness.

Conclusions—XR-NTX and BUP-NX differ considerably in their characteristics and clinical management; no studies to date have compared XR-NTX with buprenorphine maintenance. Study design choices and compromises inherent to a comparative effectiveness trial of distinct treatment regimens are reviewed.

Keywords

extended-release naltrexone; buprenorphine-naloxone; opioid dependence; medication assisted therapy; methods or experimental design; Clinical Trials Network

Introduction and Background

Opioid dependence (opioid use disorder) is a chronic relapsing disorder, conveying serious risks including disability, incarceration, blood-borne infections, and overdose fatalities. Prescription opioid and heroin use and overdose deaths have increased markedly in the US over the last two decades.[1] Mu opioid receptor agonist therapies – methadone and buprenorphine-naloxone (BUP-NX), both US Food and Drug Administration (FDA) approved for the treatment of opioid dependence through opioid maintenance – are effective as community-based treatment in promoting and sustaining abstinence from other opioids and reducing associated risks.[2-5] Naltrexone (NTX), a mu opioid receptor antagonist, blocks the effects of opioids without producing any opioid effects or physical tolerance. The effectiveness of NTX is limited by the need to fully detoxify to avoid precipitating withdrawal, and poor adherence to daily oral NTX.[6-8] Implantable and long-acting injectable forms of NTX circumvent the adherence problem, and have been efficacious in clinical trials.[7-9] Extended release NTX (XR-NTX) was FDA-approved in 2010 for the prevention of relapse to opioid dependence following detoxification following completion of a pivotal efficacy trial.[10]

Despite such solid evidence favoring long-term medication treatment for opioid use disorders, detoxification and/or short-term residential treatment episodes followed by outpatient counseling-only aftercare remain mainstays of US opioid disorder treatments.[11] Many patients believe that they can “go it alone” following detoxification, or otherwise reject agonist maintenance due to stigma, side effects and inconvenience.[12,13] Clinicians, treatment programs, and patients often espouse a strong tradition of “drug-free,” abstinence-oriented treatment, and maintenance on an opioid agonist is often not considered abstinence.[14] There are concerns about agonist diversion. Agonist maintenance is frowned upon in some settings (e.g., criminal justice settings) and in some countries (e.g., Russia).[15]

In the US, methadone is only available through specially licensed clinics and BUP-NX is only available as of May, 2016, through physicians who have completed buprenorphine waiver training. No such restrictions apply to XR-NTX, which has instead been constrained by medication costs and insurance coverage, a specialty pharmacy distribution system, a limited number of experienced providers, and by a "detoxification hurdle" (discussed below).

With effective office-based agonist (BUP-NX) and antagonist (XR-NTX) approaches available, what information is needed to increase utilization and help patients, families and providers decide on a treatment path? Agonists and antagonists are diametrically opposite in domains ranging from pharmacology to treatment philosophy (Table 1). Agonists maintain physical tolerance and opioid dependence; antagonists block any opioid effects and are not psychoactive or habit-forming. Detoxification must precede antagonist induction; no such hurdle precludes starting an agonist. Withdrawal signs and symptoms follow agonist discontinuation; there are no physiological consequences of stopping antagonist treatment. Agonists pose a significant diversion risk; not the case with antagonists which have no abuse potential. Controlled substance restrictions complicate agonist prescribing; there are none for antagonists. Some agencies, states and countries prohibit agonists; antagonists are generally more acceptable.

No large comparative effectiveness studies have evaluated XR-NTX opioid treatment outcomes compared to an agonist maintenance standard of care. Is one approach better than the other? Which approach is better for which patient (treatment matching)? What demographic, clinical and genetic features moderate treatment response? What are the economic costs, cost-effectiveness and cost-benefits of the two approaches? There is currently virtually no evidence-base to guide patients, families and providers. The purpose of CTN-0051 is to help develop such an evidence-base and to study the implementation of XR-NTX and BUP-NX into real-world community treatment settings. A wider goal is to foster more widespread adoption of opioid pharmacotherapies.

Research Design and Study Population

Study Design

CTN-0051 is an N=600, multi-site, two-arm, 6-month (24-week), parallel-group, open-label, randomized controlled trial to examine the comparative effectiveness of XR-NTX versus BUP-NX (Fig. 1). Candidates are individuals seeking treatment for opioid dependence (heroin or prescription opioid use disorders), who do not require opioids for chronic pain, and who are admitted to an inpatient (detoxification and/or short term residential treatment) program. The study is conducted in 8 community-based treatment programs (CTPs) that provide (or partner with) inpatient opioid detoxification services and can maintain participants opioid free for 3-7 days, as well as provide medication assisted therapy and at least one group and/or individual counseling session per week during the study. XR-NTX is administered by injection on an approximately every-four-week basis; BUP-NX is provided for take-home daily sublingual dosing. BUP-NX is initially dispensed weekly, then every two weeks, then every four weeks. Medical management clinician visits for all participants are on a similar schedule (weekly, then bi-weekly, then monthly). Medical management

aftercare and psychosocial referrals for both treatment arms are similar. Research visits occur weekly, until relapse criteria are met, for collection of urine samples and safety and other assessments. The primary outcome measure is the time to the event of opioid relapse, defined as >7 consecutive days of non-study opioid use or >1 day of use during each of 4 consecutive weeks, based on weekly urine samples and self-report as measured by the Timeline Follow-Back (TLFB), beginning 21 days or later post-randomization. Follow up research visits are conducted 7 and 9 months following randomization (1 and 3 months following the end of study treatment for those who complete the full 6 months).

Research Aims and Hypotheses

The primary aim of the study is to estimate the difference, if one exists, between XR-NTX and BUP-NX in the distribution of the time to relapse (i.e., loss of persistent abstinence) during a 6-month treatment trial. Our primary hypothesis is that the two treatments are similarly effective at maintaining participants relapse-free. Secondary objectives are to compare XR-NTX vs. BUP-NX on related outcomes, including successful medication induction, safety and overdose events, opioid abstinence, tobacco, alcohol and other drug misuse, cravings, mood symptoms, HIV risk behaviors, and in-treatment changes in cognitive function. Additional secondary aims are to explore baseline demographic, clinical, and genetic features as predictors of treatment success over the 6-month treatment phase (main effect of predictors), and as moderators of differential treatment effect (moderator by treatment interaction) and to collect a limited dataset to permit analyses of economic costs and benefits of the two treatments.

Protocol Development, Design Issues, and Alternative Study Designs

CTN-0051 was conceived and proposed as an effectiveness trial of XR-NTX opioid relapse prevention in community settings. Several key issues and alternative designs were considered during a 1-2 year protocol development process involving the Lead Node, the CTN Protocol Development Committee, and CTN Executive Leadership. A core issue was the appropriate comparative condition for XR-NTX within a comparative effectiveness trial and the role for current community “treatment as usual” (TAU).[16-19] Two comparator conditions, BUP-NX maintenance and detoxification followed by counseling-only, were considered.

‘XR-NTX vs. Detoxification Followed by Counseling-Only’ was the first design considered; enthusiasm was limited by the poor safety profile and questionable ethics of a no medication condition, given that the pivotal XR-NTX trial had already demonstrated the inferiority of detoxification followed by no medication, and despite the fact that counseling-only opioid treatment remains a predominant standard of care in many communities in the United States. A ‘Three-Arm XR-NTX vs. Detoxification/Counseling-Only vs. BUP-NX’ design added the eventual final comparison between XR-NTX and BUP-NX, an effective standard medication treatment, but maintained the disadvantages of a counseling-only condition. A ‘Two-Arm XR-NTX vs. BUP-NX with SMART Design (Sequential Multiple Assignment Randomized Trial)’ was considered, in which patients would be initially randomized, then re-randomized in the event of relapse.[20] Susan Murphy, an expert in SMART design, was engaged as a consultant. This design provided a protocol-driven “rescue” for patients who relapse, which

enhanced safety. And, it yielded more knowledge than the simple 2-arm trial, of a type that is particularly appropriate for effectiveness research. Concerns about the SMART design included the added expense, feasibility (how many relapsed patients could be located and agree to continue with secondary randomization?), and lack of power in the secondary randomizations. Finally, 'Patient Preferences and Choice Designs' took into account the fact that patients typically have strong preferences regarding particular opioid treatments,[21,22] and statistical methods such as propensity score comparisons can allow for valid, non-random comparisons across a treatment cohort. Preference designs were eliminated due to concerns about internal validity and losing the definitive benefits of randomization; treatment preference is assessed as a covariate prior to randomization in the current trial.

Final Design Considerations—Ultimately, it was decided to implement a 2-arm comparison of active medications, XR-NTX versus BUP-NX. This design had a favorable risk/benefit ratio and was felt to address the most important effectiveness question, comparing the new treatment (XR-NTX) to a current evidence-based standard (BUP-NX) in community-based treatment settings. Final design considerations included:

Rescue Protocol: Clinical management after a relapse, or after successful completion of the 6-month treatment phase, an important safety consideration, is not protocol-driven, but rather left to clinical judgment within routine clinical care. Nonetheless, post-study-treatment data (i.e., data on treatment after the end of up to six months of study-treatment, or relapse if occurring earlier) are collected to document subsequent treatments and their outcomes, providing some naturalistic data along the lines of a registry, and upon which to begin to address questions about longer-term algorithms of patient management.

Outpatient or Inpatient Induction: BUP-NX induction is relatively simple, requiring only that a patient progress to a mild state of opioid withdrawal before initiating BUP-NX, and is typically accomplished on an outpatient basis. XR-NTX induction of an opioid-dependent patient requires a complete detoxification and opioid washout period, which is much more difficult for outpatients to accomplish. Thus, the typical platforms for XR-NTX and BUP-NX induction greatly differ. This led to considerable deliberation about how to choose the clinical setting for randomization and induction and how to "level the playing field" to achieve a fair comparison between the two medications, particularly with regard to a relapse prevention focus (rather than an induction success focus).

One option considered was to evaluate and randomize on an outpatient basis, then hospitalize only as needed—most BUP-NX patients would not need an inpatient stay, most XR-NTX patients would. This would allow BUP-NX full flexibility in its clinical application, but would probably bias against XR-NTX since hospitalization is a hurdle that some patients would not want to accept. Members of the protocol development team who were running community based treatment programs argued that patients often present to inpatient/residential treatment before any medication options are considered, and that initiation of BUP-NX after inpatient admission was clinically credible, and an option that programs should be offering as part of routine clinical practice, but typically were not at the time of the initiation of this trial. Hence it was decided that patients would be recruited for the trial from inpatient detoxification/residential treatment settings.

Timing of Randomization: The next question was when to randomize patients. To recruit and randomize patients as soon as possible after admission to the inpatient unit would be most clinically credible and true to usual treatment, since BUP-NX could be easily initiated within a day or two of admission. This could be viewed as putting XR-NTX at a disadvantage, since naltrexone induction could take a week or more. Thus, one option considered was to require all potential trial participants to fully detoxify and wash out, in essence requiring all participants to be ready to start naltrexone, before randomization to either XR-NTX or BUP-NX. However, this was felt to be biasing the trial in favor of XR-NTX, placing unnecessary constraints on the initiation of BUP-NX and antithetical to an effectiveness trial, which seeks to test treatments as they would actually be used in clinical practice. Thus, it was decided that randomization could occur as soon as possible after admission to inpatient/residential treatment, and timing of randomization—whether early (early in detoxification where BUP-NX could be initiated, but before XR-NTX could be initiated, or late (at a point where detoxification and washout are complete and either medication could be started)—would be recorded as a covariate. An interim analysis, based on comparing success of medication induction between the two arms among patients randomized early (where BUP-NX might be expected to show more successful inductions) is described further below.

Study Team and Sites—CTN-0051 is a multi-site trial sponsored by the National Institute on Drug Abuse through the Clinical Trials Network (CTN). The CTN Greater New York Node is the Lead Node; Lead Investigator, John Rotrosen MD. Statistical analysis, data management, safety, and quality monitoring are provided by The Emmes Corporation (Rockville, MD). Study sites are community-based addiction treatment programs associated with the CTN, selected according to the following criteria: 1) provide or partner with opioid detoxification services (inpatient/residential), 2) have the capacity to initiate patients onto XR-NTX and BUP-NX, 3) have the capacity to maintain participants on XR-NTX and BUP-NX on an outpatient basis for the duration of the 24-week trial, 4) have a sufficient flow of patients completing detoxification and who do not routinely receive long-term medication-assisted therapy so as to provide a sufficient population of potential participants to achieve study enrollment goals, and 5) can provide a minimum level of outpatient counseling (at least one group and/or individual counseling session per week) for 24 weeks.

The site selection process initially solicited from each CTN Node potential community treatment programs. Sites had to meet the general criteria, above, and there was some preference for sites where access to medication-assisted treatment (MAT) after detoxification was generally limited. Geographic (site location) and ethnic (site patient populations) diversity were considered. Thirty-four individual sites applied; 16 advanced to an interview, and 10 were ultimately selected. Budget considerations then mandated further reductions to the 8 final sites. The participating CTPs selected are Bellevue Hospital Center, NY, NY (Greater NY Node), Maryhaven, Inc., Columbus, OH (Ohio Valley Node), Recovery Center of Kings County/Evergreen Treatment Services, Seattle, WA (Pacific Northwest Node), Gateway Community Services, Inc., Jacksonville, FL (Florida Node Alliance), Stanley Street Treatment and Resources, Inc., Fall River, MA (New England Consortium Node), Tarzana Treatment Centers, Tarzana, CA (Pacific Region Node),

Turquoise Lodge Hospital, Albuquerque, NM (Southwest Node), and Avery Road Treatment Center, Rockville, MD (Mid-Atlantic Node). Some of the characteristics of the eight sites at the time of site selection are shown in Table 3.

Study Population and Inclusion/Exclusion Criteria

Study eligibility criteria were developed to recruit a representative sample of treatment seeking opioid dependent patients, with minimal exclusionary criteria, consistent with generalizability goals of an effectiveness trial. Participants are ~600 treatment-seeking heroin-and/or prescription opioid-dependent volunteers, without chronic pain requiring opioid therapy, who are willing to accept either “agonist-based” or “antagonist-based” therapy. These criteria encourage enrollment of essentially all patients who would consider both XR-NTX and BUP-NX induction during a detoxification admission.

Inclusion Criteria are: 1) male or female; 2) 18 years of age and older; 3) meet DSM-5 criteria for opioid-use disorder (heroin and/or prescription opioids); 4) have used opioids other than as specifically prescribed within thirty days prior to consent; 5) seeking treatment for opioid dependence and willing to accept “agonist-based” or “antagonist-based” therapy; 6) in good-enough general health, as determined by the study physician on the basis of medical history, review of systems, physical exam and laboratory assessments, to permit treatment with XR-NTX or BUP-NX; 7) able to provide written informed consent; 8) able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study; 9) if female of childbearing potential, be willing to practice an effective method of birth control for the duration of participation in the study.

Exclusion criteria are: 1) serious medical, psychiatric or substance use disorder that, in the opinion of the study physician, would make study participation hazardous to the participant or compromise study findings or would prevent the participant from completing the study, 2) LFTs (ALT, AST) greater than 5 times upper limit of normal; 3) suicidal or homicidal ideation that requires immediate attention; 4) known allergy or sensitivity to buprenorphine, naloxone, naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or other components of the Vivitrol® diluent; 5) maintenance on methadone at doses of 30mg or greater at the time of signing consent; 6) presence of pain of sufficient severity as to require ongoing pain management with opioids; 7) pending legal action or other reasons that might prevent an individual from completing the study; 8) if female, currently pregnant or breastfeeding, or planning on conception; 9) body habitus that, in the judgment of the study physician, precludes safe intramuscular injection of XR-NTX (e.g., BMI>40, excess fat tissue over the buttocks, emaciation).

Recruitment Procedures

Most participants are recruited directly in-person by the research team on the detoxification unit and had no knowledge of the study prior to the detox admission. Additional recruitment efforts vary per site and are used as needed; these include site staff education and distribution of study materials, community or participant-level outreach and advertisements, and the encouragement of word-of-mouth referrals among potentially eligible outpatients, who are then directed to seek detoxification admission and subsequent study enrollment.

During (or prior to) the first several days of an index admission, clinical and/or research staff provide information about the study to interested, potential participants. At any point after admission candidates may begin the written informed consent and screening procedures. The timing of consent and screening is flexible, and allows sites to customize recruitment, screening, and randomization procedures to accommodate local conditions.

Randomization

Randomization is stratified by 1) treatment site, and 2) baseline opioid use (high level use [≥6 bags or equivalent intravenous (IV) heroin/day during the 7 days prior to admission] vs. all others [i.e., <6 IV bags or equivalent heroin/day during the 7 days prior to admission and all non-IV opioid users]), using a centralized, automated block assignment plan. Level of opioid use was chosen as a stratification factor because it had been shown to be the clinical characteristic most consistently predictive of outcome of naltrexone treatment, with higher level opioid use prior to admission associated with lower likelihood of successful treatment with naltrexone.[23-25]

As noted above in the discussion of design options considered, timing of randomization after admission was left flexible, and it was anticipated that this might be an important prognostic variable. Induction of active users onto an antagonist is a longer and more complicated process than agonist induction. Persons randomized later in a detoxification course and further from their last opioid use will likely have a higher rate of successful induction onto naltrexone, while this matters less for buprenorphine treatment. When the study was initially designed, an interim analysis plan (below) addressed the possibility that successful medication induction may differ across arms, particularly for those randomized early in the course of detoxification. All cases are classified into one of three groups at the time of randomization, those: (a) randomized within 24 hours of last (licit or illicit) opioid use, (b) randomized between 24 and 72 hours following last (licit or illicit) opioid use, (c) randomized more than 72 hours following last (licit or illicit) opioid use. Each of these groups represents different clinical scenarios commonly encountered in CTN CTPs. Group (a) represents early decision-making, at such a time as to avoid unnecessary detoxification for those choosing BUP-NX. For group (b), decision-making occurs later during detoxification, but while patients still need to surmount the detoxification hurdle to begin XR-NTX. Group (c) includes patients who are more fully detoxified, with some or all opioids washed out of their systems, and can be more readily inducted onto either medication, albeit with potential further delays for XR-NTX induction (in some cases, particularly following methadone or buprenorphine detoxification, a patient's urine may not be clear of opioids for up to two weeks after the last dose).

Detoxification Protocols

Opioid detoxification approaches vary widely across the US treatment system, and vary across the participating study sites, from clonidine-based, agonist-free protocols, to 3 to 5-day methadone tapers, to 3 to 14-day buprenorphine tapers. Agonist-based approaches are associated with superior detoxification outcomes (reduced withdrawal symptoms, retention),[26] but prolong induction onto XR-NTX. Rapid naltrexone induction protocols are under study, but not yet common community practice.[27,28] The protocol development team

ultimately decided to allow the detoxification method to vary according to TAU at each site. Allowing variation in detoxification methods according to TAU affords exploratory descriptive analysis by site. Further, mandating a particular detoxification method is logistically problematic since it requires programs to change their practices across all patients, not just those entering the trial. Sites are encouraged to implement the study protocol as best and as effectively as they see fit in the context of their standard detoxification approaches. The detoxification admission, medications, and nursing and psychosocial treatments are not study-provided and are the responsibility of the patient, facility, and relevant payers. However, usual care may take into account potential study participation and be adjusted by the care team as appropriate. For instance, a methadone taper may be curtailed more quickly than usual and clonidine dosing increased if a patient plans study enrollment and subsequent induction onto either XR-NTX or BUP-NX. Suggested guidelines for initiation of BUP-NX and of XR-NTX under different detoxification and timing-of-randomization scenarios (e.g. starting from a methadone taper; starting from a buprenorphine taper) are provided to sites. Weekly conference calls, led by lead team physicians (JDL, JR, EVN), are held with the sites to discuss detoxification and induction cases and ongoing clinical management. Data on detoxification, including number of days on the unit and medications received, are collected and will be compared by site and treatment assignment.

XR-NTX Induction and Maintenance

Participants randomized to XR-NTX must have completed a recent opioid detoxification, be ≥3 days removed from the last dose of opioid agonist (heroin, prescription opioids, methadone or buprenorphine), have a urine toxicology negative for the extended opioid spectrum, including methadone and buprenorphine, and have a negative naloxone challenge (>0.8mg IV, SC, or IM) to be inducted onto study medication. Induction (administration of the first XR-NTX injection) is encouraged as soon as possible following randomization and fulfillment of these post-detoxification criteria, but may occur at any time until week 22 of the study treatment phase, including following discharge if the participant leaves the unit prior to induction and relapse does not occur.

XR-NTX injections are monthly (up to 6 injections total, approximately every 4 weeks, with the final injection occurring no later than week 22). XR-NTX (4cc, ~380mg of naltrexone base) is administered in the form of Vivitrol®, purchased by the NIDA contractor for distribution to the sites, is provided to participants free of charge. XR-NTX injections may take place <4 weeks apart if there is clinical concern about non-adherence (e.g., inconsistent visit attendance), or if clinical observation is that opioid craving and/or use re-emerge during the 4th week after the last injection; however, time between injections should be at least 21 days. XR-NTX is administered by intramuscular injection to the buttocks (alternating sides) according to the injection preparation and administration procedures specified in the Vivitrol® product package insert.[29] Repeated XR-NTX injections are provided on a 4-week schedule (or after a longer interval if a participant has missed a dose). If opioid use has occurred and physical opioid re-dependence is suspected, but the relapse outcome criteria have not been met, a participant must undergo a repeat naloxone challenge and/or repeat the initial detoxification and induction procedures. Study XR-NTX is otherwise discontinued

following a relapse event, at the end of the study's active treatment phase, or as safety concerns or patient preference dictates. Patients preferring long-term XR-NTX treatment are referred to community providers, if available.

BUP-NX Induction and Maintenance

Buprenorphine-naloxone is provided as Suboxone® sublingual film, 4mg/1mg and 8mg/2mg strengths. BUP-NX is donated to the study by Reckitt-Benckiser (now Indivior PLC), distributed by the NIDA contractor and dispensed to participants free of charge. BUP-NX induction proceeds according to the initial detoxification approach: 1) participants randomized during a buprenorphine-based detoxification will continue on buprenorphine and be converted to a daily maintenance dose range of 8-24mg/day, 2) participants randomized during a methadone-based detoxification will be inducted onto BUP-NX 24-48hrs following the last methadone dose, or after withdrawal symptoms have clearly emerged, 3) participants randomized during a non-opioid-based detoxification or after completing a buprenorphine- or methadone-based detoxification may be inducted onto BUP-NX immediately or after a sufficient delay since last agonist dose.

Maintenance doses of BUP-NX from 8mg-24mg are typical in community treatment and this is the target dose range (higher or lower maintenance doses are allowed if clinically appropriate). For all BUP-NX participants, from Day 7 through week 24, daily doses may be titrated to minimize BUP-NX related AEs, minimize cravings, and in response to any intermittent illicit opioid use/lapse. BUP-NX is dispensed to participants at induction (Week 0) and at treatment weeks 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 20, though the protocol allows sites to vary this dispensing schedule when clinically indicated. Patients preferring long-term BUP-NX maintenance are encouraged to continue treatment with non-study providers once study BUP-NX is discontinued. Study BUP-NX is discontinued following a relapse event, at the end of the study's active treatment phase, or as safety concerns or patient preference dictates. Once discontinuation is planned, the study may dispense a further two-week supply of BUP-NX, allowing participants to taper off or transition to a non-study prescriber for long-term maintenance. These general office-based approaches to BUP-NX are generally consistent with current recommendations for office-based buprenorphine maintenance, such as the American Society of Addiction Medicine National Practice Guidelines.[30]

Medical Management

At each study visit patients receive Medical Management (MM) clinical support from their study clinicians. MM was developed for the NIAAA COMBINE study comparing combinations of medications and counseling methods for treatment of alcohol dependence [31], and was adapted for this trial of medication treatment of opioid dependence. MM sessions focus on: 1) establishing and maintaining patient-clinician rapport and partnership, 2) education surrounding opioid addiction and treatment, 3) establishing and maintaining a plan for adherence to XR-NTX monthly or BUP-NX daily medication, 4) advice and encouragement to maintain abstinence from opioids and other drug and alcohol, 5) monitoring medication side effects and dose adjustments, and, 6) encouraging adherence to the psychosocial treatment plan, including counseling, 12-step involvement, and further community-based treatment. MM also provides guidelines for assessment and management

of relapse in both arms, and allows for study clinicians to prescribe ancillary medications common in opioid treatment. Fidelity to MM is not rigorously assessed, although standardized provider training took place prior to study start, weekly conference calls with providers focus on MM issues, standardized progress notes prompting clinicians to address each MM item, and standard operating procedures offer ongoing guidance to clinicians and the study teams on adherence to MM. MM visit schedules are the same for both arms, initially weekly (weeks 0-4), then every two weeks (weeks 4-16), and finally every four weeks (weeks 16, 20, 24). Unscheduled or additional MM visits may be conducted as needed. For all participants a final MM visit will take place on week 24 although no medication will be dispensed (except a final two-week BUP-NX supply if indicated).

Psychosocial Counseling Referrals

Psychosocial counseling consists of outpatient counseling and is encouraged during MM. Participation is voluntary and not considered study treatment. All participating sites offer at least a minimum level of non-study outpatient psychosocial care consisting of at least one group and/or individual counseling session per week for up to 24 weeks. Data are collected from the participant on counseling sessions attended. Failure to enroll or attend counseling sessions does not affect study participation, study medications, or MM treatment.

Study Assessments

The full schedule of study assessments is included as Table 5. Screening and baseline assessments capture participant demographic, medical, psychiatric, drug use, and treatment history, quality of life and current health status, in addition to blood and urine testing. Treatment phase assessments include weekly monitoring of self-reported opioid and other drug use, urine samples, cravings, adverse events (AR) and serious adverse events (SAE), including self-reported overdose events, and non-study treatments. During-treatment feasibility and process measures include Medical Management visit attendance, XR-NTX dose logs, BUP-NX dose levels and daily adherence per self-reported, counts of returned medication, and urine buprenorphine testing. Longer-term, post-treatment assessments occur at weeks 28 and 36, and assess safety in the initial weeks and months following discontinuation of XR-NTX or BUP-NX. These assessments specifically address concerns about the potential of overdose deaths after XR-NTX discontinuation and the criticism leveled at the FDA for approving XR-NTX indication without such data.[32,33] Non-fatal self-reported overdose events and deaths are queried using standard AE/SAE forms and reviewed by the NIDA Medical Monitor. Events are coded as drug/alcohol overdose per source documentation (e.g. change in mental status, respiratory distress, naloxone reversal, or death in the context of drug/alcohol use).

Primary and Secondary Outcomes

The primary aim of the study is to estimate the difference, if one exists, between XR-NTX and BUP-NX in the distribution of the time to relapse (i.e., loss of persistent abstinence) during the 6-month trial. The primary outcome measure is the time to the relapse event. By definition individuals are abstinent from non-detox, non-study opioids at the time of randomization. Relapse, or loss of persistent abstinence from non-study opioids, occurs when the participant has used non-protocol prescribed opioids starting at day 21 post-

randomization as follows: 1) four consecutive opioid use weeks, or 2) seven consecutive days of use by self-report. A use week is defined as any week during which a participant self-reports at least one day of non-prescribed opioid use, provides a urine sample positive for non-study opioids, or fails to provide a urine sample at the weekly assessment visit. In the event that a participant reports no use, but their urine test indicates use, the week is considered a use week. Missing urine samples resulting from missed visits or refusal are classified as positive. The time of the event occurs at the start of the qualifying clinical event period (e.g., first of the 7 consecutive use days or start of the 4 consecutive weeks of use).

The choice of primary outcome for this trial was complicated by the fact that the presumed failure modes differ between XR-NTX and BUP-NX. Patients typically do not use opioids while naltrexone is in the system, due to the blockade of opioid effects. Thus, treatment failure on XR-NTX takes the form of a binary relapse event--the patient skips the next scheduled dose (4 weeks past the last dose), then relapses to regular opioid use at the point that the blockade wears off, often by 5 or at most 6 weeks after the last dose. At that point naltrexone cannot be restarted until another detoxification is completed. With BUP-NX on the other hand, patients may move relatively easily back and forth between adherence to BUP-NX and taking heroin or other illicit opioids, resulting in a pattern of persistent opioid positive urines in the presence of adherence or partial adherence to medication. Ultimately it was decided that sustained abstinence without relapse to regular opioid use represented an embodiment of what most clinicians would consider a good clinical outcome for both treatments. It is a simple, clinically meaningful outcome measure, which is desirable for the purposes of an effectiveness trial. Further, many patients leaving a detox unit recently or newly inducted onto either medication will ‘test’ or ‘lapse’ by using illicit opioid misuse, only to find the maintenance treatment medication now prevents the effective use of heroin or prescription opioids. Due to this common scenario, as well as the fact that detox methadone may persist in a BUP-NX participant's urine for some time, the primary relapse event outcome can only begin at day 21 post-randomization.

Secondary outcomes compare XR-NTX to BUP-NX as follows: 1) proportion successfully inducted onto assigned medication, 2) safety, as measured by adverse events and serious adverse events, including opioid overdose episodes, 3) opioid abstinence, as measured by self-reported days using opioids and urine samples, 4) misuse of tobacco, alcohol, other drugs, 5) craving for opioids and other drugs, 6) depressive, anxiety, and subacute withdrawal symptoms, 7) problems related to drug misuse, 8) HIV risk behaviors, and, 9) in-treatment cognitive function (Table 2). Additionally, baseline factors, including genetic markers, will be assessed as predictors of main effects and as moderators of differential treatment effects (treatment interactions). An ancillary study will use data collected in this study to compare cost and cost effectiveness by treatment.

Data and Safety Monitoring—A NIDA CTN Protocol Review Board reviewed the protocol during development, and a NIDA CTN Data Safety and Monitoring Board (DSMB) monitors the trial on a regular basis. The DSMB examines accumulating safety, trial performance and outcome data to ensure the safety of study participants and the integrity of the trial. Additionally, a NIDA-assigned Medical/Safety Monitor oversees safety and evaluates all Adverse Events (AEs), including overdose events.

Statistical Analysis

Power and Sample Size—Meta-analyses of randomized controlled trials of BUP-NX maintenance treatment for opioid dependence suggest that approximately 50% of patients are retained in BUP-NX treatment with good clinical outcomes similar to our 'non-relapse' definition over 6 months. [3,4] In the XR-NTX pivotal trial [10], 53% received all monthly injections and were retained for 6 months. Using those assumptions, the 95% confidence interval (CI) width for the hazard ratio of the difference between treatments (BUP-NX versus XR-NTX) for the 50th percentile decreases by 11% when the sample size increases from 200/arm to 250/arm and narrows only slightly with the addition of 50/arm. Thus, the substantial additional cost of adding more participants per group was not worth the marginal gains in the CI width, and we selected 200/arm as the target sample.

Sample Size Adjustments following Interim Analysis—From the outset, a key design consideration revolved around how to preserve the study's relapse prevention focus in the context of posited differential study medication induction success. We hypothesized that induction success (receipt of the initial dose of study medication) would be greater for patients randomized to BUP-NX than it would be for patients randomized to XR-NTX, and that these differences would be particularly exaggerated amongst those randomized early in detoxification (those who still have opioids in their system). Further, it was assumed that patients not inducted would have overall poorer outcomes (increased relapse risk) than those receiving medication. The initial protocol addressed this through flexible consent and randomization timing and a mitigation plan that modified entry criteria if in fact a marked difference in induction success was seen early in the trial. In essence this was a design compromise that enabled the trial to definitively answer both the differential induction success rate question and the relapse prevention question. The initial protocol called for an interim analysis of induction success after enrollment of the first 100 "early randomizers" i.e., patients randomized within 72 hours of their last dose of any opioid. If differential induction success rates were observed in the "early randomizers", there would be a change in enrollment criteria, which would restrict the study population to only "late randomizers". Further, the plan called to increase the overall sample size to achieve a large enough sample of late randomizers. A problem with this initial plan was that it basically stopped the initial study design in mid-stream, changed the entry criteria and, in effect, created two separate studies. What was not known at the outset of the study was what the ratio of late randomizers to early randomizers would be once all of the study sites were initiated, but at the time the study approached reaching enrollment of the first 100 early randomizers this ratio was approximately 2:1. This enabled us to retain initial entry criteria, preserve a single study, and preserve the comparative effectiveness focus by revising the approach to data analysis rather than changing the trial design. More detail on analysis and sample size implications is presented in the following sections.

The interim analysis plan compares the induction success rates in early randomizers between the two treatment arms. The decision rule has >80% power (alpha=2.5% 1 tail) to identify differences of .25 or greater if the true initiation rate for the BUP-NX arm is in the expected range (>=.85). In the revised protocol, if the induction success rate is significantly different between the two treatments, then recruitment will continue until 350 late randomizers have

been enrolled, and the data analysis plan will be amended to incorporate the interaction between timing of randomization and treatment group (see Primary Outcome Analysis section for details). This will increase the total sample size to N=~600. 350 late randomizers (n=175 per group) was considered close enough to the 400 (n=200 per group) originally planned to yield a very similar (only slightly wider) 95% confidence interval. This will preserve the intent to achieve a relatively precise estimate of the difference in relapse rates among late randomizers.

Primary Outcome Analysis—The initial analysis will be the construction of the asymptotic 95% CI for the hazard ratio of the difference between the treatment arms in the time to event distribution for the primary outcome. The study arm success rates with confidence intervals at week 24 and the difference in success rate at that time point and associated confidence intervals will be constructed. The binary baseline variable of early vs. later randomization (as previously defined) is included in the primary outcome analysis as a covariate. The early vs. late randomization covariate by treatment interaction is included in the primary analysis. If the covariate (early vs. late randomization) by treatment interaction is significant ($p < 0.10$) then the interaction term is retained in the final model. To characterize the interaction, the effect of treatment assignment is estimated separately in early vs. late randomizers, and these two separate estimates become the primary findings of the study.

Subsequent analyses will explore the treatment effect as a function of time, stratification variables and other factors that may be moderators, having differential impact on treatment success. The analyses will first model the time to event primary outcome measure as a function of treatment assignment (XR-NTX vs. BUP-NX), opioid dependence severity stratum and site in a proportional hazards regression model. The constancy of the relative hazard assumption will be examined via the interaction of treatment and time, and the interaction between treatment and baseline severity will be tested. Secondary analyses of the week-24 successes will include screening baseline variables to identify potential subgroups in the XR-NTX group with differential results.

Secondary Outcome Analyses—Successful initiation of protocol therapy is an important binary outcome that may also be useful to subsequently explain differences in the primary outcome. Most other secondary outcome analyses will follow a similar form and strategy to that above, with different linear models as appropriate for the form of the secondary outcome variable: dichotomous secondary outcomes will use logistic regression; time-to-event variables will use survival analysis with Cox models; continuous variables or count variables (e.g., bags per day of heroin use) will use mixed effect models depending on the distribution of the outcome (e.g., normal, Poisson, negative binomial, zero-inflated). Repeated measures will have time in the model in addition to treatment and baseline variates. Exploratory analyses will mainly involve exploring baseline demographic and clinical variables, and candidate genetic markers, as predictors of success, or as moderators of differences in success between XR-NTX and BUP-NX. Some during-treatment variables will also be of interest to explore as potential mediators of outcome. For example, opioid use during treatment has been shown to predict relapse in naltrexone, mainly use after

discontinuing naltrexone ("unblocked use"), but also repeated episodes of use while on naltrexone ("blocked use").[24,34] Dysphoria, or subacute withdrawal symptoms during treatment would also be of interest as a mediator of outcome. For these analyses, the variables would be entered into the primary outcome model, or select secondary outcome models, as time-dependent covariates, examining the impact on the size of the coefficient of the treatment effect, or covariate by treatment interactions. Mediators could also be examined separately in the XR-NTX and BUP-NX groups.

Interim Safety and Efficacy Analyses—The study undergoes safety monitoring by a NIDA-constituted DSMB. Both therapies are standard therapies with regulatory approval for treatment of opiate dependence. The treatment strategies have not been directly compared before. Classic interim safety and efficacy monitoring is not planned as both are considered acceptable therapies. The adaptive strategy for addressing substantial differential treatment induction rates among early randomizers is described above. Continuing the study until 350 individuals are included in the main analysis group (late randomizers) will assist better understanding of personalized therapeutic strategies by making possible precise secondary assessments and identification of subgroups that differentially benefit.

Missing Data and Dropouts—Dropout from treatment is a typical failure mode for the treatment of opioid dependence with both XR-NTX and BUP-NX. As a result, when defining the primary outcome for this study, it was determined that missed study visits would contribute missing=positive weekly urine results. Therefore, there will be no missing data for the primary outcome since the imputation of the missing values is implicit in the primary outcome definition. In particular for the primary endpoint, individuals who withdraw or drop-out will be considered relapse events once they fail to provide four consecutive weekly urine specimens. Intensive tracking efforts are made to retain all participants through all scheduled research visits, independent of their status on study medication.

Other outcome variables (opioid and other substance use over time, craving, mood, etc.) will have missing data due to missed visits and dropout from treatment and from study participation. The generalized linear model, or mixed effects model frameworks that will be used for analyses, works with what data are gathered, and assumes missing data are missing at random. For selected secondary outcome analyses, sensitivity analyses will be considered to examine the stability of estimated treatment effects in the face of departures from the assumption of missing at random. Aggressive tracking procedures will be put into effect to attempt to locate participants and re-engage them, and to minimize missing data.

Ancillary Studies

Genetics Study—An ancillary genetics study is underway with data collection as part of the parent trial including a biological sample and Family Origin questionnaire which collects information about the participant and her/his biological family members' race/ethnicity, place of birth and ancestry. Other data collected as part of the parent protocol will be used in the analyses including: treatment outcomes, DSM-5, Addiction Severity Index Lite, Hamilton Depression Scale (17 item), Fagerström Test for Nicotine Dependence, and Risk

Assessment Battery, among others. Consent for the genetics study is included in the consent for the parent trial. DNA extraction and storage takes place at the NIH/NIDA Center for Genetics Studies Repository. Analyses will be conducted at the Laboratory on the Biology of Addictive Diseases at The Rockefeller University (PI: Mary Jeanne Kreek).

The primary goal of the genetics study is to determine if there is a significant relationship between any of the functional variants in three genes (*OPRM1*, *OPRK1* and *PDYN*) and differences between XR-NTX and BUP-NX in the distribution of the time to relapse (i.e., loss of persistent abstinence) during the 6-month study. Secondary goals of the genetics study are to determine if there are significant relationships between any of the functional variants in three genes (*OPRM1*, *OPRK1* and *PDYN*) and outcomes on XR-NTX and BUP-NX for the following domains (based on assessments used for secondary outcomes in the parent protocol): 1) opioid abstinence, as measured by the Timeline Follow-Back (self-report days using opioids), proportion of opioid-positive urine tests; 2) misuse of alcohol and other drugs of abuse (e.g., cocaine, other stimulants, cannabis, benzodiazepines) by self-report and urine drug screens; 3) tobacco use as measured by the Fagerström Test for Nicotine Dependence (FTND); and 4) depressive, anxiety, and subacute withdrawal symptoms (typical constellation is fatigue, anorexia, and insomnia) as measured by the Hamilton Depression Scale (17-item) and the Subjective Opioid Withdrawal Scale.

Health Services and Economics Study—An ancillary health services and economics study is also underway with participant level data collected as part of the parent study, including assessment of non-study medical and other services (NMS) and quality of life (EQ-5D). Other data collected as part of the parent protocol will be used in the analyses. In addition, site level data will be collected by the Health Services study team. Analyses of these and national level data is led by Bruce Schackman, PhD, at the Center for Health Economics of Treatment for Substance Users at Weill Cornell Medical College.

Aims are to: 1) estimate and compare the economic costs of opioid dependence treatment with XR-NTX and BUP-NX from the perspectives of the treatment provider, the payer, and the patient; 2) estimate and compare quality-adjusted life year (QALY) outcomes for opioid dependence treatment with XR-NTX and BUP-NX; 3) from a societal perspective, evaluate the incremental cost-effectiveness and cost-benefit of opioid dependence treatment with XR-NTX compared to BUP-NX; and 4) conduct an exploratory evaluation of the potential cost-effectiveness of pre-treatment testing for genetic variants (e.g. OPRM1, OPRK1, PDYN) associated with responses to opioid dependence treatment with XR-NTX or BUP-NX.

Results

Three sites began recruitment in Jan/Feb, 2014, with the remaining 5 sites initiating the study in staggered fashion between June and September, 2014. Recruitment completed in May, 2016, with N=772 participants consented, N=570 randomized (N=352 of them late randomizers). As of July 25, 2016, N=436 have completed the study (or are past the window for the final follow up visit). To date, the only substantial change from the original protocol was the change in sample size from ending enrollment at N=400 total to ending enrollment

after 350 late randomizers which will yield a total N=600 following the amended analysis plan described above.

Discussion

XR-NTX opioid relapse prevention therapy is the most recently US approved medication treatment for opioid use disorders, yet many aspects of its use in community settings are not well understood. The goal of this trial is to provide a comparison of usual XR-NTX maintenance outcomes compared to a BUP-NX standard of care among a general US adult opioid dependent population following voluntary admission for inpatient opioid detoxification. This is in keeping with a core mission of the National Institute on Drug Abuse Clinical Trials Network to investigate effectiveness, foster dissemination, and expand community treatment options using efficacious addiction pharmacotherapies. Expanding the use of medication treatments for opioid disorders is a public health priority in the face of the current prescription opioid and heroin addiction and the US overdose epidemic.

The comparative effectiveness two-arm design dispenses with a placebo- or counseling-only comparison. As summarized, the XR-NTX pivotal trial in Russia, an earlier, smaller, placebo- and dose-controlled efficacy trial,[7] and now a recently published large NIDA-funded multi-site XR-NTX vs. Treatment-As-Usual (TAU) criminal justice-focused outpatient study (NCT00781898),[35] have all shown XR-NTX is superior to placebo or TAU. We also considered a methadone maintenance comparison, however methadone can only be used in a licensed opioid treatment program whereas both buprenorphine and naltrexone are available for office-based opioid treatment and as such are adaptable within a range of outpatient programs. Buprenorphine products have since 2002 become the most common, most prescribed form of opioid medication treatment in the US. This strongly favors office-based BUP-NX maintenance as the ideal comparison condition.

The choice to focus on recruitment from detoxification and not outpatient settings was made to center the trial on two realities: the continued extensive use of acute detoxification for opioid treatment in the US, and the lack of use of medication maintenance strategies during immediate aftercare. Detoxification and short-term residential units are excellent environments in which to manage opioid withdrawal and induct patients onto either XR-NTX or BUP-NX, and a post-detoxification comparative effectiveness trial should yield externally valid and generalizable data regarding the routine community use of XR-NTX. Further, while BUP-NX induction is simpler than XR-NTX induction among active heroin or prescription opioid users, retention in BUP-NX community maintenance treatment is far from ideal with most studies reporting a 6-month retention of 50% or much less, including patients struggling with on-going use and positive urine samples while on BUP-NX.[36-38] It is therefore possible that while XR-NTX is more difficult to initiate for most active opioid users, overall rates of retention and of urines negative for non-study opioids at 6 months may compare quite favorably to agonist standard of care. Nonetheless, results from this trial will not be immediately generalizable to the initiation of either medication on an outpatient basis or in primary care settings.

Within a comparative effectiveness design, the study contrasts two medications from different classes (a mu opioid receptor antagonist, XR-NTX vs. a partial agonist, BUP-NX) with very different preparations (monthly extended-release by injection vs. daily sublingual self-administration), representing fundamentally opposed pharmacologic and practical treatment approaches (opioid-free relapse prevention vs. maintenance of physical opioid dependence). The design problems encountered and the alternative solutions considered in the effort to construct a level playing field and a useful comparison may be informative for the design of other comparative effectiveness trials contrasting treatments that differ enough from each other to constitute different regimens.

Our site selection process yielded 8 sites with high-volume inpatient detox units, a large proportion of opioid admissions, a high likelihood of implementing the two medications on the detox unit and then as outpatient Medical Management, and an overall environment of clinical research competence. This clearly makes the trial most generalizable to settings and practices most similar to these 8 sites and their regions and to programs amenable to our specific treatment protocols. Programs mandating a higher level of intensive outpatient program attendance (which is in this trial voluntary), or only initiating XR-NTX on an outpatient basis, for instance, would be pursing different methods of XR-NTX implementation. Further research would ideally continue to map best practices for sustaining and further expanding both buprenorphine and naltrexone treatments.

Some further limitations are clear. An open-label, non-blinded design compares the treatments as they are delivered under real world conditions. This is consistent with the emphasis on external validity characteristic of an effectiveness trial. However, this does potentially allow for attention or assessment biases compared to a placebo-controlled, blinded efficacy design. Our primary outcome is a dichotomous definition of a opioid relapse event, consisting of 7 or more consecutive days of opioid use or 4 consecutive ‘use weeks,’ marked by 1 or more day or use or a positive or missing urine sample. An emphasis on such a yes/no, success/failure, outcome, may ignore important overall reductions in opioid use from baseline, such as significantly fewer bags of heroin used per day or fewer days of use per week. Such reduced but persistent use will still contribute to a relapse outcome and trigger an end to study medication treatment. This may not reflect standard and therapeutically sound approaches to opioid maintenance treatment, which typically allow for and support the patient through similar relapse episodes without discontinuing treatment. We will otherwise examine both in-treatment and post-study rates of opioid use as an important secondary outcome.

These limitations notwithstanding, there exists little or no evidence-base to help patients with opioid use disorders, their providers, and families make rational choices between opioid antagonist and agonist medication treatments. Findings from CTN-0051 should address this gap. It is our hope that the results of this trial will provide valuable information to the field about the comparative effectiveness and associated treatment matching strategies for BUP-NX and XR-NTX. This is critical because they are the two major pharmacotherapies for opioid addiction that could be most easily and widely initiated in the real world setting of community detoxification in inpatient/residential treatment, which remains an essential

mainstay component of the continuum of care, and where the use of both should become part of the standard of care.

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References

1. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies--tackling the opioid-overdose epidemic. The New England journal of medicine. 2014; 370:2063–6. [PubMed: 24758595]
2. Kreek MJ, Borg L, Ducat E, Ray B. Pharmacotherapy in the treatment of addiction: methadone. J Addict Dis. 2010; 29:200–16. [PubMed: 20407977]
3. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. The Cochrane database of systematic reviews. 2008:CD002207. [PubMed: 18425880]
4. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. The Cochrane database of systematic reviews. 2014; 2:CD002207.
5. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. The Cochrane database of systematic reviews. 2009:CD002209. [PubMed: 19588333]
6. Nunes EV, Rothenberg JL, Sullivan MA, Carpenter KM, Kleber HD. Behavioral therapy to augment oral naltrexone for opioid dependence: a ceiling on effectiveness? The American journal of drug and alcohol abuse. 2006; 32:503–17. [PubMed: 17127538]
7. Comer SD, Sullivan MA, Yu E, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Archives of general psychiatry. 2006; 63:210–8. [PubMed: 16461865]
8. Krupitsky E, Zvartau E, Blokhina E, et al. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. Archives of general psychiatry. 2012; 69:973–81. [PubMed: 22945623]

9. Tiihonen J, Krupitsky E, Verbitskaya E, et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. The American journal of psychiatry. 2012; 169:531–6. [PubMed: 22764364]
10. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011; 377:1506–13. [PubMed: 21529928]
11. Stein BD, Gordon AJ, Sorbero M, Dick AW, Schuster J, Farmer C. The impact of buprenorphine on treatment of opioid dependence in a Medicaid population: recent service utilization trends in the use of buprenorphine and methadone. Drug and alcohol dependence. 2012; 123:72–8. [PubMed: 22093488]
12. Rieckmann T, Daley M, Fuller BE, Thomas CP, McCarty D. Client and counselor attitudes toward the use of medications for treatment of opioid dependence. Journal of substance abuse treatment. 2007; 32:207–15. [PubMed: 17306729]
13. Fox AD, Maradiaga J, Weiss L, Sanchez J, Starrels JL, Cunningham CO. Release from incarceration, relapse to opioid use and the potential for buprenorphine maintenance treatment: a qualitative study of the perceptions of former inmates with opioid use disorder. Addiction science & clinical practice. 2015; 10:2. [PubMed: 25592182]
14. Rieckmann TR, Kovas AE, McFarland BH, Abraham AJ. A multi-level analysis of counselor attitudes toward the use of buprenorphine in substance abuse treatment. Journal of substance abuse treatment. 2011; 41:374–85. [PubMed: 21821379]
15. Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. Current psychiatry reports. 2010; 12:448–53. [PubMed: 20640538]
16. Brigham GS, Feaster DJ, Wakim PG, Dempsey CL. Choosing a control group in effectiveness trials of behavioral drug abuse treatments. Journal of substance abuse treatment. 2009; 37:388–97. [PubMed: 19553062]
17. Carroll KM, Ball SA, Jackson R, et al. Ten take home lessons from the first 10 years of the CTN and 10 recommendations for the future. The American journal of drug and alcohol abuse. 2011; 37:275–82. [PubMed: 21854269]
18. Nunes EV, Ball S, Booth R, et al. Multisite effectiveness trials of treatments for substance abuse and co-occurring problems: have we chosen the best designs? Journal of substance abuse treatment. 2010; 38(1):S97–112. [PubMed: 20307801]
19. Feaster DJ, Mikulich-Gilbertson S, Brincks AM. Modeling site effects in the design and analysis of multi-site trials. The American journal of drug and alcohol abuse. 2011; 37:383–91. [PubMed: 21854281]
20. Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SA. A “SMART” design for building individualized treatment sequences. Annual review of clinical psychology. 2012; 8:21–48.
21. Bailey GL, Herman DS, Stein MD. Perceived relapse risk and desire for medication assisted treatment among persons seeking inpatient opiate detoxification. Journal of substance abuse treatment. 2013; 45:302–5. [PubMed: 23786852]
22. Stein MD, Anderson BJ, Bailey GL. Preferences for Aftercare Among Persons Seeking Short-Term Opioid Detoxification. Journal of substance abuse treatment. 2015; 59:99–103. [PubMed: 26254317]
23. Sullivan MA, Rothenberg JL, Vosburg SK, et al. Predictors of retention in naltrexone maintenance for opioid dependence: analysis of a stage I trial. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2006; 15:150–9.
24. Carpenter KM, Jiang H, Sullivan MA, et al. Betting on change: modeling transitional probabilities to guide therapy development for opioid dependence. Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors. 2009; 23:47–55. [PubMed: 19290689]
25. Brooks AC, Comer SD, Sullivan MA, et al. Long-acting injectable versus oral naltrexone maintenance therapy with psychosocial intervention for heroin dependence: a quasi-experiment. The Journal of clinical psychiatry. 2010; 71:1371–8. [PubMed: 20673549]

26. Ling W, Amass L, Shoptaw S, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. Addiction. 2005; 100:1090–100. [PubMed: 16042639]
27. Sigmon SC, Bisaga A, Nunes EV, O'Connor PG, Kosten T, Woody G. Opioid detoxification and naltrexone induction strategies: recommendations for clinical practice. The American journal of drug and alcohol abuse. 2012; 38:187–99. [PubMed: 22404717]
28. Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. Jama. 2005; 294:903–13. [PubMed: 16118380]
29. Alkermes I. Vivitrol Product Package Insert and Medication Guide. 2013
30. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Journal of addiction medicine. 2015; 9:358–67. [PubMed: 26406300]
31. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. Jama. 2006; 295:2003–17. [PubMed: 16670409]
32. Wolfe DC, Dasgupta N, Bruce RD, Wodak A. Authors' Reply. Lancet. 2011; 378:666.
33. Wolfe D, Carrieri MP, Dasgupta N, Wodak A, Newman R, Bruce RD. Concerns about injectable naltrexone for opioid dependence. Lancet. 2011; 377:1468–70. [PubMed: 21529930]
34. Sullivan MA, Garawi F, Bisaga A, et al. Management of relapse in naltrexone maintenance for heroin dependence. Drug and alcohol dependence. 2007; 91:289–92. [PubMed: 17681716]
35. Lee JD, Friedmann PD, Kinlock TW, et al. Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. The New England journal of medicine. 2016; 374:1232–42. [PubMed: 27028913]
36. Lee JD, Grossman E, DiRocco D, Gourevitch MN. Home buprenorphine/naloxone induction in primary care. Journal of general internal medicine. 2009; 24:226–32. [PubMed: 19089508]
37. Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. JAMA internal medicine. 2014; 174:1369–76. [PubMed: 25090173]
38. Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medication-assisted treatment for opiate dependence: A systematic review. J Addict Dis. 2016; 35:22–35. [PubMed: 26467975]
39. Trivedi MH, Wisniewski SR, Morris DW, et al. Concise Health Risk Tracking scale: a brief self-report and clinician rating of suicidal risk. The Journal of clinical psychiatry. 2011; 72:757–64. [PubMed: 21733476]
40. Sobell, JL., Sobell, MB. Timeline Follow-Back: A technique for assessing self-reported alcohol consumption. In: Litten, R., Allen, J., editors. Measuring Alcohol Consumption. The Human Press Inc.; 1992.
41. Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. J Consult Clin Psychol. 2000; 68:134–44. [PubMed: 10710848]
42. McLellan AT, Kushner H, Metzger D, et al. The Fifth Edition of the Addiction Severity Index. Journal of substance abuse treatment. 1992; 9:199–213. [PubMed: 1334156]
43. Hamilton M. A rating scale for depression. Journal of neurology, neurosurgery, and psychiatry. 1960; 23:56–62.
44. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. The American journal of drug and alcohol abuse. 1987; 13:293–308. [PubMed: 3687892]
45. Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. Journal of behavioral medicine. 1989; 12:159–82. [PubMed: 2668531]
46. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. British journal of addiction. 1991; 86:1119–27. [PubMed: 1932883]

47. Navaline HA, Snider EC, Petro CJ, et al. Preparations for AIDS vaccine trials. An automated version of the Risk Assessment Battery (RAB): enhancing the assessment of risk behaviors. AIDS research and human retroviruses. 1994; 10(2):S281–3. [PubMed: 7865319]

48. Sanchez-Cubillo I, Perianez JA, Adrover-Roig D, et al. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. Journal of the International Neuropsychological Society : JINS. 2009; 15:438–50. [PubMed: 19402930]

49. Jensen AR, Rohwer WD Jr. The Stroop color-word test: a review. Acta psychologica. 1966; 25:36–93. [PubMed: 5328883]

50. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of medicine. 2001; 33:337–43. [PubMed: 11491192]

51. van der Zanden BP, Dijkgraaf MG, Blanken P, de Borgie CA, van Ree JM, van den Brink W. Validity of the EQ-5D as a generic health outcome instrument in a heroin-dependent population. Drug and alcohol dependence. 2006; 82:111–8. [PubMed: 16168573]

52. Wallihan DB, Stump TE, Callahan CM. Accuracy of self-reported health services use and patterns of care among urban older adults. Med Care. 1999; 37:662–70. [PubMed: 10424637]

53. Harlow SD, Linet MS. Agreement between questionnaire data and medical records. The evidence for accuracy of recall. Am J Epidemiol. 1989; 129:233–48. [PubMed: 2643301]

54. Roberts RO, Bergstralh EJ, Schmidt L, Jacobsen SJ. Comparison of self-reported and medical record health care utilization measures. J Clin Epidemiol. 1996; 49:989–95. [PubMed: 8780606]

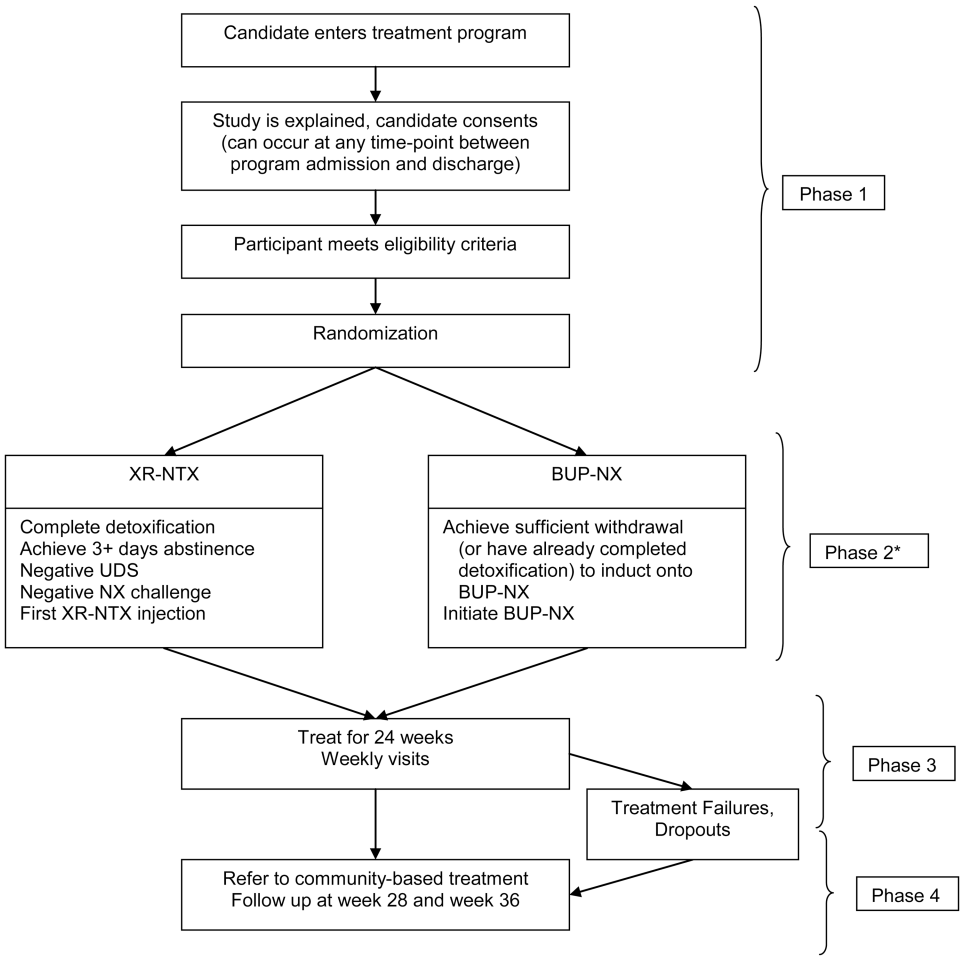

Figure 1. Study Schema

*The window for induction remains open into Phase 3 (until week 22).

Table 1
Comparison of Agonist vs. Antagonist Medication Assisted Treatment Approaches

	Agonist	Antagonist
Treatment Strategy / Philosophy	Opioid Maintenance	Opioid Blockade
Detoxification Hurdle for Induction	No *	Yes
Withdrawal on Drug Discontinuation	Yes	No
Diversion Risk	Yes	No
Acceptability	Rejected by Some Patients, States, Countries, Agencies	Generally Acceptable Not Widely Embraced **
Controlled Substance	Yes	No
Extended-release Formulations	Yes	Yes
Indicated for Alcohol Dependence	No	Yes
Contraindicated if Chronic Opioids for Pain	No	Yes

* Initiation of Buprenorphine, a partial agonist, does require that patients be in at least the early stages of withdrawal in order to avoid precipitated withdrawal, but this is relatively easy to achieve clinically. An antagonist like Naltrexone in contrast is likely to precipitate withdrawal unless the patient is fully detoxified.

** There are contingents of clinicians who discourage antagonist treatment, holding that agonist is superior. This is partly related to the idea that opioid dependence may represent an endogenous deficit in opioid signaling that needs to be corrected with opioid substitution

Table 2
Protocol Primary and Secondary Outcomes and Hypotheses

Primary Outcome	**Hypotheses**
Time to opioid relapse	XR-NTX will produce similar time-to-relapse vs. BUP-NX
Secondary Outcomes	Hypotheses
Proportion successfully inducted onto assigned study medication (binary: did or did not receive first dose of XR-NTX, or achieve maintenance dose of BUP-NX)	BUP-NX will produce higher rate of successful induction than XR-NTX\Significance/Rationale: XR-NTX induction requires completion of detoxification, whereas BUP-NX induction only requires onset of withdrawal symptoms. Thus XR-NTX may have more dropouts after randomization but prior to XR-NTX induction.
Adverse Events related to study medications	XR-NTX and BUP-NX will produce equivalent rates of SAEs, and equivalent rates of AEs, though AE pattern will differ somewhat (e.g. injection site reactions with XR-NTX)\Significance/Rationale: Careful documentation of SAEs and AEs, including overdose episodes, would be considered essential safety data, and important component of a comparative effectiveness trial.
Opioid abstinence over time while on study medication (Weekly TLFB, confirmed by urine drug screens)	XR-NTX will produce greater opioid abstinence than BUP-NX\Significance/Rationale: XR-NTX produces complete blockade of opioid effects, so that during treatment with monthly injections, opioid use can be expected to be minimal. In contrast BUP-NX may not produce complete blockade, or patients may reduce or stop doses for a few days and substitute other opioids (heroin, prescription opioids).
Alcohol and other drug use, over time (TLFB and UDS)	XR-NTX will be superior to BUP-NX in producing abstinence from alcohol and other drugs \Significance/Rationale: Clinical trials show XR-NTX is effective for treatment of alcohol dependence, and naltrexone has some evidence of efficacy for stimulant dependence.
Cigarette smoking (FTND, Tobacco Use Questionnaire, VAS nicotine craving)	XR-NTX will reduce cigarette smoking compared to BUP-NX\Significance/Rationale: Naltrexone has been studied as a treatment for nicotine dependence, with some support from clinical trials, although inconsistent. Given high co-prevalence in opioid-nicotine disorders, a comparative advantage of one or the other of these treatments at reducing smoking would be valuable to examine.
Opioid Craving (VAS) over time	XR-NTX will be superior to BUP-NX in reducing opioid craving\Significance/Rationale: Pivotal XR-NTX trial [10] showed, surprisingly, that XR-NTX reduced craving substantially compared to placebo.
Subacute withdrawal symptoms over time (HAM-D, SOWS)	XR-NTX will produce greater severity of subacute withdrawal symptoms than BUP-NX during the first month after randomization, but will be equivalent to BUP-NX in months 2 to 6\Significance/Rationale: Low-grade withdrawal-like symptoms (dubbed “naltrexone flu” by the Columbia group, and consisting typically of insomnia, fatigue, and anorexia, though not drug craving) have been observed in some patients in the 1 to 4 weeks after naltrexone initiation, resolving gradually. Further characterization of this syndrome would be important for developing treatment guidelines.
Problems related to drug abuse (ASI-Lite and EQ-5D)	XR-NTX will be superior to BUP-NX\Significance/Rationale: Greater opioid and non-opioid abstinence on XR-NTX will result in fewer problems associated with active drug abuse.
HIV risk behavior over time (RAB and other HIV risk measures)	XR-NTX and BUP-NX will be equivalent\Significance/Rationale: The opioid-dependent population is at high risk for HIV, both from injection drug use and from unsafe sexual practices. Effective treatment for the opioid dependence may reduce HIV risk behavior. Given the high morbidity and mortality associated with HIV, a comparative advantage of one or the other of these treatments would be valuable to examine.
Cognitive function (Trails Making Test Parts A and B, Stroop)	XR-NTX and BUP-NX will be equivalent\Significance/Rationale: Some providers and policy-makers are concerned that patients maintained on BUP-NX will have opioid-agonist-related cognitive impairment.

Table 3

Site Characteristics (at time of site selection)

Site	Detoxification methods	Opioid detoxification admissions per year n	Discharges without induction onto medication treatment[1] n (%)	Length of stay in detox mean days (min/max)	Demographics	Facility type
1	Methadone taper Buprenorphine taper	695	569 (81.9%)	3 (1-5)	M/F: 96%/4% Hispanic: 30% White: 28% AA: 38%	Hospital
2	Buprenorphine taper	1152	1151 (99.9%)	7 (3-21)	M/F: 66%/34% Hispanic: 2% White: 82% AA: 17%	Drug treatment
3	Buprenorphine taper	358	233 (65.1%)	15	M/F: 52%/48% Hispanic: 63% White: 91% AA: 2%	Hospital
4	Methadone taper Buprenorphine taper	1511	1441 (95.4%)	6.5 (5-14)	M/F: 66%/34% Hispanic: 18% White: 73% AA: 4%	Drug treatment
5	Methadone taper	2039	1994 (97.8%)	5 (4-7)	M/F: 57%/43% Hispanic: 6% White: 66% AA: 29%	Drug treatment
6	Non-opioid (clonidine)	1460	1422 (97.4%)	5 (5-7)	M/F: 67%/33% Hispanic: 6% White: 76% AA: 10%	Drug treatment
7	Non-opioid (clonidine)	526	507 (96.4%)	5 (3-7)	M/F: 62%/38% Hispanic: 3% White: 90% AA: 8%	Drug treatment
8	Buprenorphine taper	425	225 (52.9%)	22 (3-28)	M/F: 72%/28% Hispanic: 6% White: 59% AA: 30%	Drug treatment

[1]Medication treatment: methadone, buprenorphine (BUP-NX), naltrexone.

Table 4

Study Treatments Visit Schedule

Study Week	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Medical Management Visits (both arms)		x	x	x	x	x		x		x		x		x		x		x				x				x
XR-NTX Administration		x*	x*	approximately every 4 weeks, final injection occurring no later than week 22																						
BUP-NX Dispensing		x	x	x	x	x		x		x		x		x		x		x				x				x~

x* = the timing of the initial XR-NTX dose depends on the length of time needed to complete detoxification and achieve an opioid-negative urine sample

x~ = for BUP-NX taper where indicated

Table 5

Schedule of Study Assessments (Need to Add Citations here or in text for validated instruments)

Assessment	Frequency
Informed consent and medical release	Baseline
General measures:	
Inclusion/exclusion	Baseline, confirmed just prior to randomization
Locator form	Baseline, then every 4 weeks
Demographics form	Baseline
Motivations, attitudes & expectations form	Baseline
Treatment satisfaction survey	EOT/Week 24
Relapse assessment	Weekly beginning after Day 21
Continuing treatment forms	EOT/Week 24
Study termination form	EOS/Week 36
Safety and medical measures:	
Medical and psychiatric history	Baseline
Physical exam, vitals	Baseline, EOM/Week 24 (if inducted)
DSM-5 criteria	Baseline
Concise Health Risk Tracking-Self Report (CHRT-SR)[39]	Baseline, Induction, MM visits
Clinical laboratory tests	Baseline, LFTs at Weeks 4, 12, EOM/24 (if inducted)
Pregnancy and birth control assessment	Baseline, Weeks 4, 8, 12, 16, 20, EOM/24
Adverse events and serious adverse events	At each study visit
Injection site examination	Baseline and first post-injection visits
Compliance measures:	
Dose logs	Each visit following induction
Medical management log	Each MM visit (scheduled and unscheduled)
Psychosocial participation log	Weeks 1 through 24
Outcome measures:	
Timeline Follow-Back (TLFB)[40,41]	At each study visit
Urine drug screen (UDS)	At each study visit
Addiction Severity Index-Lite (ASI-Lite)[42]	Baseline, EOT/Week 24, Week 36
Visual analog scales	Baseline, opioid craving at each study visit, others every 4 weeks
Hamilton depression scale (17 item) (HAM-D)[43]	Baseline, Weeks 1, 2, 3, 4, 8, 12, 16, 20, EOT/Week 24, 28, 36
Subjective opioid withdrawal scale (SOWS)[44]	Baseline, Induction, Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 36
Fagerström Test for Nicotine Dependence (FTND)[45,46]	Baseline
Risk Assessment Battery (RAB)[47]	Baseline, Weeks 12, EOT/Week 24, 36
Cognitive function: Trail making tests[48], Stroop[49]	Baseline, Weeks 4, 8, 16, EOT/Week 24
Detoxification utilization form	Baseline
Health Services measures:	

Assessment	**Frequency**
EuroQol (EQ-5D)[50,51]	Baseline, Weeks 4, 8, 12, 16, 20, EOT/Week 24, 28, 36
Non-medical and other services (NMS)[52-54]	Baseline, Weeks 4, 8, 12, 16, 20, EOT/Week 24, 28, 36
Genetics measures:	
Genetics sample	Baseline
Family Origin questionnaire	Baseline

EOM=end of medication
EOT= end of treatment
EOS=end of study