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Surmounting Withdrawal to Initiate Fast Treatment with Naltrexone (SWIFT): A stepped wedge hybrid type 1 effectiveness-implementation study

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Ethics approval and consent to participate

This study was approved by Biomedical Research Alliance of New York (BRANY), submission 20-PRS-526. Informed consent was obtained from all relevant participants.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2023.107148.

Data availability

No data was used for the research described in the article.

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Abstract

Background: Extended-release injectable naltrexone (XR-NTX) is an effective treatment for opioid use disorder (OUD), but initiation remains a barrier to implementation. Standard practice requires a 10- to 15-day inpatient admission prior to XR-NTX initiation and involves a methadone or buprenorphine taper followed by a 7- to 10-day washout, as recommended in the Prescribing Information for XR-NTX. A 5- to 7-day rapid induction approach was developed that utilizes low-dose oral naltrexone and non-opioid medications.

Methods: The CTN-0097 Surmounting Withdrawal to Initiate Fast Treatment with Naltrexone (SWIFT) study was a hybrid type I effectiveness-implementation trial that compared the effectiveness of the standard procedure (SP) to the rapid procedure (RP) for XR-NTX initiation across six community inpatient addiction treatment units, and evaluated the implementation process. Sites were randomized to RP every 14 weeks in an optimized stepped wedge design. Participants (target recruitment = 450) received the procedure (SP or RP) that the site was implementing at time of admission. The hypothesis was RP will be non-inferior to SP on proportion of inpatients who receive XR-NTX, with a shorter admission time for RP. Superiority testing of RP was planned if the null hypothesis of inferiority of RP to SP was rejected.

Discussion: If RP for XR-NTX initiation is shown to be effective, the shorter inpatient stay could make XR-NTX more feasible and have an important public health impact expanding access to OUD pharmacotherapy. Further, a better understanding of facilitators and barriers to RP implementation can help with future translatability and uptake to other community programs.

Trial Registration: NCT 04762537 Registered February 21, 2021.

Keywords

Opioid use disorder; Extended-release injectable naltrexone; Rapid induction procedure; Stepped wedge design; Hybrid effectiveness-implementation trial; Clinical trials network

1. Introduction

The opioid epidemic continues apace with over 100,000 drug overdose deaths in 2021, the majority related to opioids [1,2]. The three FDA-approved medications for opioid use disorder (MOUD) are the full opioid receptor agonist methadone, partial agonist buprenorphine, and antagonist naltrexone in extended-release injection formulation (XR-NTX). These medications are highly effective when taken as directed, promote abstinence from opioids, and protect against overdose [3–6]. Yet, the majority (78%) of individuals with opioid use disorder (OUD) are not on medication [1,7]. There is an urgent need to close this gap and scale up MOUD implementation. Recent large trials have shown that monthly XR-NTX injection, once initiated, is similar in effectiveness to daily sublingual buprenorphine maintenance [6,8], yet XR-NTX is the least utilized MOUD [9]. XR-NTX may be optimal for patients who seek relapse-prevention without opioid agonist treatment, or who have not responded well to previous trials of buprenorphine or methadone.

An important barrier to implementation of XR-NTX is the "induction hurdle," namely that patients need to be withdrawn from opioids before initiating naltrexone to avoid precipitated withdrawal [10]. Current standard practice involves a 3- to 5-day taper of methadone or buprenorphine followed by a 7- to 10-day opioid-free period (washout) as recommended by the XR-NTX (Vivitrol®) Prescribing Information [11]. During this prolonged regimen, patients may struggle with opioid withdrawal or have difficulty remaining inpatient for other reasons and drop out of treatment. Evidence suggests XR-NTX initiation is more successful on an inpatient basis, where patients can be closely monitored and access to non-prescribed opioids is limited, particularly for more severely dependent patients [12]. However, longer (10- to 15-day) inpatient admissions are often not supported by third-party payors, nor well tolerated by patients.

Rapid procedures (5–7 days) for XR-NTX initiation have been developed and utilize the minimal necessary dose and duration of buprenorphine (typically one day), more aggressive use of non-opioid medications to manage withdrawal (i.e., clonidine and benzodiaze-pines), and gradual titration of low-dose oral naltrexone. Such rapid procedures have demonstrated feasibility and effectiveness in several trials [13–16], but have not been compared to the longer, standard approach on inpatient units in a large trial. We describe the methodology for a hybrid type I effectiveness-implementation trial conducted within the National Institute on Drug Abuse's National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) comparing the standard 10- to 15-day procedure (SP) for XR-NTX initiation to a rapid 5- to 7-day procedure (RP), in an optimized stepped wedge design [17]. The hypothesis was that RP will be non-inferior to SP on the primary outcome of proportion of patients initiated onto XR-NTX while inpatient, while requiring substantially fewer days from admission to XR-NTX initiation. Secondary implementation objectives focused on process evaluation and general feasibility and acceptability of RP. The larger goal was to develop a preliminary implementation facilitation package that could be tested in future trials and disseminated.

2. Methods

2.1. Overview of design and objectives

The NIDA CTN-0097 Surmounting Withdrawal to Initiate Fast Treatment with Naltrexone (SWIFT) study (NCT 04762537) was a hybrid type I effectiveness-implementation trial supported by the National Institutes of Health HEAL Initiative®. Patient recruitment (target of 450 participants) was conducted over 70 weeks at six community inpatient addiction treatment programs. Site randomization followed an optimized stepped wedge design with one site randomly selected at the start of the study to implement RP for the entirety of the trial [17] (Table 1). The remaining five sites implemented SP, or treatment as usual, at the start of the study. Sites were notified of RP randomization 8 weeks prior to active enrollment and started preparations for RP (pre-implementation phase). Participant enrollment for SP was still active during this 8-week preparatory phase. After 14 weeks of RP implementation (one step), one of the remaining five programs stepped into RP implementation, and that was repeated until five of the six sites were implementing RP. The remaining sixth site implemented SP for the entire study.

The primary effectiveness objective was to compare the 10- to 15-day SP to the novel 5- to 7-day RP on the primary outcome of inpatient XR-NTX initiation with the hypothesis that RP was non-inferior to SP. Superiority testing for RP was planned if the null hypothesis of inferiority of RP to SP was rejected. Secondary aims compared RP and SP on other clinical outcomes including time to receipt of first XR-NTX injection while inpatient, opioid cravings and withdrawal, adverse events, retention in study for second and third XR-NTX injections, and opioid and other substance use. Additional objectives were to explore participants' baseline demographics and clinical features as predictors of XR-NTX initiation and other clinical outcomes.

This was a hybrid type 1 effectiveness-implementation trial thus the implementation process was evaluated secondary to the primary clinical effectiveness aim [18,19]. Implementation objectives included identifying barriers and facilitators to implementation and exploring promising strategies for RP implementation, with a larger goal of developing a preliminary implementation facilitation package for future testing and dissemination.

2.2. Site selection

Six sites were selected from sixteen NIDA CTN-affiliated community addiction treatment programs that applied to CTN-0097. Selected sites afforded geographic distribution across the United States (rural Pacific Northwest, rural Midwest, urban South-Central, urban Southeast, and suburban Mid-Atlantic and Northeastern regions). Site eligibility criteria included: ability to provide opioid detoxification services with inpatient or residential treatment stays for at least 14 days (to accommodate the standard procedures for XR-NTX initiation), offered a standard 10- to 15-day XR-NTX induction with buprenorphine taper followed by washout period, ability to provide follow-up outpatient care (medical management and counseling) and subsequent XR-NTX injections for at least 2 months after XR-NTX induction, ability to enroll 1–2 patients with OUD per week over the 70-week recruitment period, ability to enroll underinsured patients with the support of study funds, diverse patient population with respect to an adequate representation of women and minorities, capacity to provide evaluation and treatment for co-occurring psychiatric disorders or provide treatment referrals, agree to implement RP as the induction method for patients attempting to transition from active opioid use to XR-NTX, and site leadership interested in adopting and implementing RP for XR-NTX initiation. Sites were excluded that had experience implementing rapid procedures for XR-NTX initiation.

2.3. Participant eligibility criteria

Eligible participants were 18 years or older, English-speaking, met Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for OUD [20], willing to undergo opioid detoxification and treatment with XR-NTX, able to consent within 4 days of admission on the inpatient unit, and were appropriate candidates for XR-NTX as per the clinician's judgment. Exclusion criteria were serious medical or psychiatric conditions, suicidal or homicidal ideation, or other severe substance use disorders precluding study participation (i.e., requiring a higher or different level of care), receiving methadone maintenance treatment within 14 days of consent, receiving buprenorphine treatment prior to admission unless poor treatment response (i.e., non-adherence or active illicit opioid

use warranting XR-NTX treatment trial), body habitus that precludes safe intramuscular injection of XR-NTX (i.e., body mass index (BMI) >40 lbs./in^2), pain requiring opioid analgesics, legal status precluding study participation, psychosocial or legal circumstances that would threaten the feasibility of an inpatient XR-NTX induction, or known allergy or sensitivity to buprenorphine, naloxone, naltrexone, or components of the Vivitrol® (XR-NTX) diluent (e.g., polylactide-co-glycolide or carboxymethylcellulose). Females planning pregnancy, pregnant, breastfeeding, or not using an effective birth control method were excluded. These criteria aimed to include a broad range of subjects to adequately reflect this patient population.

2.4. Recruitment procedures

The target recruitment was 450 participants (225 SP; 225 RP) across six sites (75 participants per site). Recruitment strategies primarily involved approaching individuals seeking treatment at sites. Additionally, sites used advertisements and encouraged word-of-mouth referrals. Recruitment occurred during the SARS-CoV-2 pandemic and site-level infection policies, unit closures, staff shortages, and weekly recruitment numbers were monitored throughout the trial. Potential candidates could be approached for study participation up to seven days prior to admission, and within four days from inpatient admission. Clinical staff evaluated patients and potential candidates for XR-NTX through a shared decision-making process for MOUD options. If determined to be a candidate for XR-NTX, research staff met with the patient and obtained study consent. Participants received the XR-NTX initiation regimen (RP or SP) that was offered on site at time of admission (Fig. 1).

2.5. Site randomization

Site randomization was managed by an independent statistician and revealed randomization one site at a time for five sites that stepped into implementing RP (Table 1).

2.6. XR-NTX initiation procedures

2.6.1. Standard Procedure (SP)—SP was intended to reflect standard clinical practice, following a guideline of a 5-day buprenorphine taper (e.g., buprenorphine 8 mg on Day 1, 6 mg on Day 2, 4 mg on Day 3, 2 mg on Day 4, 1 mg on Day 5), then an 8-day opioid-free washout period, followed by XR-NTX administration when determined eligible by naloxone or oral naltrexone challenge (Table 2). Sites and their clinicians, not the study team, were responsible for patient care. SP varied according to sites' standard clinical practices (i.e., longer opioid-free washout periods and/or variability in adjunctive medication regimens).

2.6.2. Rapid Procedure (RP)—RP involved an initial day of buprenorphine dosing up to 10 mg, a 24-hour opioid-free washout period, and a 3- to 4-day low-dose oral naltrexone titration (from 0.5 mg to 6 mg) prior to XR-NTX administration (Table 3). Sites were provided with a procedural order set which they customized to their clinical workflow. The order set detailed buprenorphine dosing, scheduled and as needed non-opioid medications for reducing withdrawal symptoms, oral naltrexone and XR-NTX dose and timing. Non-opioid adjunctive medications included scheduled and as needed clonidine, clonazepam,

antiemetics (i.e., prochlorperazine, ondansetron), sleep aids (i.e., zolpidem, trazodone), and ibuprofen and/or acetaminophen for mild pain and body aches. Opioid withdrawal symptoms were monitored using the Clinical Opiate Withdrawal Scale (COWS). Additional monitoring included vital signs, regular oral hydration with electrolyte-rich sports drinks to combat dehydration or clonidine-induced hypotension, and assessment of sedation, gait instability, and falls prevention. Buprenorphine dosing ranged from 2 mg to 10 mg, and higher doses were discouraged given the potential risk of precipitated withdrawal upon introduction of naltrexone. If patients received higher buprenorphine doses, or consecutive days of dosing, an extended opioid-free washout period could be implemented. Again, sites and their clinicians, not the study team, were responsible for patient care and exercised flexibility within RP guidelines, including shortening or extending the procedure as clinically indicated. Patient tolerability for advancing RP was determined by assessment of opioid withdrawal symptoms, with a goal of maintaining low severity or absent withdrawal symptoms during naltrexone uptitration. Conversely, if patients experienced an increase in opioid withdrawal symptoms, naltrexone titration could be extended. If a participant requested to leave the inpatient unit before initiating XR-NTX, clinicians weighed benefits of earlier XR-NTX administration and potential risks of precipitated opioid withdrawal symptoms versus offering another MOUD before inpatient discharge. Clinical staff on the units were coached to provide psychoeducational and supportive counseling on opioid withdrawal, management, medication side effects, and motivation enhancement therapy focused on adherence to induction procedures and XR-NTX initiation, or other MOUD if the participant did not pursue XR-NTX.

2.7. Post-induction procedures

Participants that did not initiate XR-NTX were encouraged to initiate and/or continue other MOUD (buprenorphine or methadone) before discharge from inpatient care. After inpatient discharge, all participants were encouraged to continue MOUD and could receive up to two additional monthly XR-NTX injections provided by the study (Fig. 1). Discharge planning included referral to the unit's affiliated outpatient service or other referrals as appropriate. Discharge counseling focused on MOUD adherence, risk of overdose for patients leaving the inpatient unit without initiating MOUD, education on potential protracted opioid withdrawal symptoms after first XR-NTX injection, and education on overdose prevention with naloxone. Discharge medications for protracted opioid withdrawal included tapered regimens of clonidine and clonazepam, antinausea medication, and sleep aids. Patients were also discharged with naloxone rescue kit(s) for opioid overdose prevention and nicotine replacement therapy for individuals with nicotine use.

Study assessment visits occurred at post-induction Weeks 1, 2, 3, 4, 6, and 8 (Fig. 1). Intensive efforts were made to contact and re-engage patients who discontinued study treatment.

2.8. Site-level implementation procedures

The uptake and implementation of RP required program-level change, intensive clinical monitoring, and development of new skills and procedures by clinical teams. Therefore, local implementation teams used different strategies to support adoption and implementation

of RP. Strategies varied based on each site's needs, staffing, and resources. Common implementation strategies employed by sites (Supplementary Table 1) included identification and preparation of local champions [21–23], forming clinical implementation teams, assessing readiness [24], identifying potential implementation barriers and facilitators [25], and dynamic training and development of clinical tools [26], train-the-trainer strategies [27–31], and as needed consultation with local clinicians or the Lead Node team [32]. The Lead Node team delivered virtual trainings for RP and conducted educational outreach visits [33] when feasible during the SARS-CoV-2 pandemic.

2.9. Assessments

The full schedule of assessments is included in Table 4. Participant assessments included baseline demographics, medical, psychiatric, drug use, treatment history, quality of life and current health status, COVID impact, motivation for treatment, and urine toxicology. Assessments during inpatient detoxification included daily monitoring of administered medications, opioid withdrawal symptoms (COWS), and vital signs harvested from the medical records. Other assessments included opioid cravings, targeted safety events (TSE), serious adverse events (SAE), and weekly monitoring of depression severity and general anxiety disorder symptoms. Fidelity to RP or SP clinical practices was assessed using a critical action checklist for each patient during the induction phase. Post-induction phase assessments included monitoring of self-reported drug use, opioid cravings and withdrawal, urine toxicology, TSEs, SAEs (including self-reported overdose events), and treatment received.

Implementation process assessments included the number of patients admitted with OUD and the proportion inducted onto XR-NTX over each 14 week step at each site (organizational level clinical data collection form), staff readiness and preparedness for RP implementation (readiness and preparedness rulers and organizational readiness to change assessment (ORCA) [34]), and organizational fidelity to implementation checklists. Qualitative assessments included evaluation of site needs, implementation process observational notes, and semi-structured qualitative staff interviews. Semi-structured interviews focused on workflow changes for implementation of RP, barriers, facilitators, sustainability considerations, and impact of COVID.

2.10. Data and safety monitoring

The NIDA CTN Protocol Review Board reviewed the protocol during development, and the NIDA CTN Data Safety and Monitoring Board (DSMB) monitored the trial examining safety, trial performance and availability of outcome data. A NIDA-assigned Medical/Safety Monitor oversaw safety and evaluated TSEs and SAEs.

2.11. Statistical analysis

2.11.1. Primary and secondary outcomes—The primary outcome measure was a dichotomous measure of treatment initiation success defined as receipt of the first XR-NTX injection while inpatient (within 30 days from admission). The 30-day time frame allowed for inclusion of participants that may have prolonged inpatient admissions for varying circumstances, although this was uncommon. Failure to initiate XR-NTX while inpatient

was subdivided for descriptive purposes into: 1) aborted the naltrexone initiation effort and initiated buprenorphine or methadone maintenance, 2) continued XR-NTX induction in outpatient setting, or 3) dropped out or discharged from the inpatient unit.

Secondary outcomes included time from inpatient admission to receipt of first XR-NTX injection, opioid cravings and withdrawal, safety events, retention in the trial to second and third XR-NTX injections, and opioid use as measured by self-reported days of opioid use and urine toxicology samples. Implementation outcomes focused on process evaluation and general feasibility and acceptability of RP (Table 5).

2.11.2. Power and sample size—CTN-0097/SWIFT was designed as an optimized stepped wedge randomized trial [17], which maximized power to determine non-inferiority of RP versus SP. The probability of successful inpatient XR-NTX initiation was assumed to be 55% in the SP arm and 70% in the RP arm, for a treatment difference of 15% [35]. The non-inferiority margin was set at 10%, which corresponded to an odds ratio of 0.67 (proportion of success in RP = 0.45, proportion of success in SP = 0.55). To conclude that RP was non-inferior to SP, the lower bound of the two-sided 95% CI for the odds ratio for RP and SP had to be above 0.67. Observations were assumed to be equally correlated within site, regardless of time period. The intraclass correlation (ICC) (i.e., the correlation between two participants within the same site) was assumed to be 0.14 based on data from a previous trial [6]. Correlated binary data were simulated using the Parzen algorithm [36]. When designing the study, sensitivity power analyses were conducted for different values of the ICC, effect sizes, and number of sites. The optimized stepped wedge design with 6 sites and 5 periods of time (steps), enrolling a total of 450 participants (15 participants per site per step), was powered at 88% to show non-inferiority of RP to SP. The power was evaluated to be 88% or more irrespective of the value of the ICC. In addition, the study was adequately powered (80% or more) to account for simulated one site drop-out, lower rates of enrollment (10% or less) or for slightly smaller treatment effects (13% or 14%). Additional simulations were conducted to assess the impact of COVID assuming one to three sites may have reduced enrollment in the first two steps at the beginning of the study. Even with these enrollment simulations, the study maintained a high power of 79 or more.

2.11.3. Primary outcome analysis—The primary outcome analysis will use a generalized linear mixed effects model with a logistic link based on Hussey and Hughes [37]. The log odds of a participant receiving the first XR-NTX injection will be modeled as a function of the procedure received (RP versus SP), time (i.e., study month or step) to control for secular trends, and a random effect for site to control for nesting of participants within site. The null hypothesis of inferiority of RP to SP will be rejected if the lower 95% confidence limit of the odds ratio of success [odds(RP)/odds(SP)] exceeds 0.67. If the null hypothesis of inferiority is rejected, then superiority of RP will be tested. Constant correlation of observations within site will be assumed regardless of time period. Sensitivity analyses of the primary outcome will be performed to account for different correlation structures (23,24). Supportive analyses related to the primary objective will include testing for a fixed effect of treatment by time interaction, which if significant, would indicate

differential impact of treatment across time. Subgroup analyses for age, sex, race, and ethnicity will be conducted.

2.11.4. Secondary outcome analysis—Secondary outcomes will be modeled using similar mixed effects methods as for the primary outcome, with the appropriate linear model for each outcome distribution.

2.11.5. Exploratory analysis—Exploratory analysis includes participant and site-level factors (such as staff knowledge and attitudes) as predictors or moderators of differences in successful XR-NTX initiation between SP and RP. Several patient-level factors are predicted to be associated with successful XR-NTX induction including severity of OUD based on route of use (intravenous (IV) use greater severity than non-IV), type of opioid (fentanyl, heroin, or prescription opioid) with fentanyl users being most severe and prescription opioid users least severe, as well as psychiatric and substance use disorder comorbidity. For the analysis, patient and site-level factors will be included in the primary outcome model (or secondary, if applicable) as covariates or covariate by treatment interactions.

2.11.6. Implementation process evaluation and qualitative analyses—Although not formally testing implementation strategies (consistent with type 1 hybrid study design), it was important to capture the implementation strategies for development of a preliminary implementation facilitation package for future replicability and testing [19,38–41]. Implementation strategies were tracked throughout the trial to the extent possible using a standardized taxonomy by Expert Recommendations for Implementation Change (ERIC) [42] and Proctor et al.'s reporting specifications [41].

Implementation outcomes will be evaluated using mixed methods analyses and the framework Reach, Efficacy, Adoption, Implementation, and Maintenance (RE-AIM) with an equity focus through comparison of patient and staff characteristics (Table 5) [43–45]. Rapid qualitative deductive analyses [46,47] will be conducted and guided by the Consolidated Framework for Implementation Research (CFIR); a conceptual framework that can be applied to organize implementation determinants across constructs: 1) intervention characteristics, 2) outer setting, 3) inner setting, 4) characteristics of individuals, and 5) implementation process [48,49].

2.11.7. Interim safety and efficacy analyses—One interim safety analysis was performed. The NIDA CTN DSMB evaluated this safety report to ensure the safety of study participants, and adequate trial performance and data collection. No efficacy interim analyses were planned for this trial.

2.11.8. Missing data and dropouts—Discontinuation of either RP or SP before receiving XR-NTX while inpatient for any reason (i.e., leaving the inpatient unit or switching to alternative MOUD) was considered induction failure for the primary outcome. Thus, the primary outcome, whether a participant received the first XR-NTX while inpatient, was not expected to have any missing data. Secondary and other outcomes (opioid and other substance use over time, craving, mood, etc.) may be missing due to missed visits,

treatment discontinuation, or drop-out from the study participation. The mixed effects model framework will use all available data under the missing at random (MAR) assumption.

2.12. Trial status

Sites were identified and participation confirmed on May 29, 2020. Site training began with the first site on January 19, 2021 and the first 14-week step began on March 16, 2021. Active recruitment of participants into either RP or SP concluded on July 19, 2022. Follow-up patient visits for the post-induction phase concluded on September 21, 2022.

3. Discussion

Key study design considerations during development of CTN-0097/SWIFT included whether to conduct the trial in the outpatient or inpatient setting, patient-level versus site-level randomization, and hybrid effectiveness-implementation design. The inpatient setting was selected given substantial evidence that the success rate of XR-NTX initiation was low in outpatient settings among patients with more severe OUD (heroin or fentanyl use, IV use) [12]; who are at highest risk for overdose and the most immediate public health imperative. Such patients, with high levels of physiological tolerance and dependence, loss of control over opioid use, and psychosocial impairment, have difficulty participating in an XR-NTX induction regimen that requires stopping illicit opioids and following an elaborate outpatient medical schedule. RP has been moderately successful in an intensive outpatient setting with the frequent medical monitoring needed to keep patients comfortable and motivated [35]. However, this model does not routinely exist in community-based practice, challenging real-world translatability and sustainability, whereas medically oriented inpatient addiction treatment units are widespread and accustomed to closer medical monitoring and drug withdrawal regimens. Further, there is a need to change practices on these inpatient units with most programs tapering opioids (“detoxification”) and fewer than 20% of patients leaving these units on MOUD [50]; a practice associated with high risk for relapse and overdose death [51–54]. Demonstration of XR-NTX initiation in this trial could help shift practices on inpatient units to MOUD initiation, including buprenorphine or methadone [51,55,56]. Hence, site clinicians were encouraged to use a shared decision-making tool that reviewed MOUD options to determine who was a candidate for XR-NTX. MOUD initiation (buprenorphine, methadone, XR-NTX) while inpatient was encouraged for all patients. Any patients that elected XR-NTX treatment, and later changed their mind or failed initiation for other reasons, were encouraged to initiate buprenorphine or methadone while inpatient.

Patient-level randomization was considered and would have been more consistent with an efficacy or effectiveness aim. At a pragmatic level, patient-level randomization did not seem feasible due to likely confusion and cross-contamination if both RP and SP were conducted at the same time. Site-level randomization was ideal and could yield a more naturalistic sample as patients seeking XR-NTX simply consent to be followed throughout the initiation procedure that the unit is implementing, rather than consenting to individual-level randomization. Additionally, there was prior evidence on feasibility and effectiveness of RP [12,15,35], and the next important step was to test implementation in the community in a hybrid effectiveness-implementation study design [18,19,39,57]. RP implementation at

the program level requires buy-in across leadership and clinical staff, a shift in practices, and differing site-level strategies to facilitate implementation. Given that these implementation strategies had not yet been studied, a hybrid type 1 effectiveness-implementation design was selected to test effectiveness on patient level outcomes (primary objective) while evaluating the implementation process (secondary objective) [18,19].

A stepped wedge randomized design was chosen rather than a parallel cluster-randomized design. The parallel group design has stronger internal validity and is not subject to threats such as secular changes in patient populations and their outcomes over time that can cloud the interpretation of stepped wedge trials [37,58]. A parallel group design would also require a larger sample of treatment programs, thus increasing cost of the trial and logistics. In comparison, the stepped wedge design required fewer resources and supported a comprehensive evaluation of the implementation process at each site, one at a time. Sites were expected to encounter different implementation challenges and employ various strategies to overcome these. It was important to capture these process data and explore implementation strategies for RP to inform development of a preliminary implementation package, and ultimately, improve translatability to naturalistic treatment settings [19,39].

The primary outcome, XR-NTX initiation while inpatient, was chosen as it seemed the most immediate, concrete aim of standard and rapid procedures. It addresses the imperative that patients with OUD do not leave the inpatient unit without starting MOUD [51,55,56]. Whether inpatient XR-NTX initiation is followed by adherence to subsequent engagement in outpatient care and monthly XR-NTX injections was also important given that patients are at risk for attrition and overdose [59], and this was included as a secondary outcome. While inpatient length-of-stay and other factors may have an impact, outpatient adherence is largely influenced by factors not under the control of the inpatient procedures, and separate studies of procedures to improve adherence to outpatient MOUD are needed.

A non-inferiority hypothesis was chosen for the primary outcome analysis, rather than superiority. We expected the RP to have a higher XR-NTX initiation success rate than SP and the estimate of the difference and its confidence limits will be presented. Prior evidence suggested the difference could be small and require a very large sample size to be confident of power to detect superiority. However, if the null hypothesis of inferiority of RP to SP is rejected, then superiority of RP will be tested. Regardless of superiority testing, RP has an inherent advantage in feasibility and cost with a shorter inpatient length-of-stay. Thus, if RP is shown to be roughly comparable in XR-NTX initiation to SP with a non-inferiority test, it could be recommended based on the shorter length of stay.

The design of the CTN-0097/SWIFT trial illustrates challenges encountered in evaluating a complex intervention along the spectrum of effectiveness to implementation. It is hoped that the findings will guide the field on how best to initiate XR-NTX, provide a better understanding of barriers and facilitators to the uptake of XR-NTX, and train clinicians and treatment programs in RP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Adam Bisaga has participated as an unpaid consultant to Alkermes, Inc., received grant funding (through the institution) from Alkermes, Inc., has served as an investigator on a multi-site clinical trial funded by Alkermes, Inc., and has received medication for NIDA-funded studies from Alkermes, Inc.

Dr. Edward V. Nunes has been a Principal Investigator or Co-Investigator on studies that received donated or discounted medication from Alkermes, Inc., Indivior Inc. (formerly Reckitt-Benckiser) and Braeburn-Camurus, Inc. (CAM-2038), and donated digital therapeutic from Pear Therapeutics and CHESS Health. Dr. Nunes has served as an uncompensated consultant to Alkermes, Inc., Braeburn-Camurus Inc., Indivior, and Pear Therapeutics. He has no relevant equity, intellectual property, compensated consulting, travel, or other arrangements with any of these entities.

Dr. John Rotrosen has been a Principal Investigator or a Co-Investigator on studies for which support in the form of donated or discounted medication, smartphone apps, and/or funds has been, or is provided by Alkermes, Inc. (Vivitrol®, extended-release injectable naltrexone), Indivior, Inc. (formerly Reckitt-Benckiser; Suboxone®, buprenorphine/naloxone combination), Braeburn-Camurus, Inc. (extended-release injectable buprenorphine), Pear Therapeutics (smartphone apps ReSET and ReSET-O), CHESS Health (Connections smartphone app), and Data Cubed (smartphone apps SOAR and mSAP-PORT). None of this support has gone, or will go, directly to Dr. Rotrosen, rather to either NYU, or to NIDA/NIH, or to NIDA's contractor Emmes, Inc. Dr. Rotrosen recently served in a non-paid capacity as a member of an Alkermes, Inc. study Steering Committee. He has no relevant equity, intellectual property, compensated consulting, travel or other arrangements with any of these entities.

Dr. Marc Fishman has served as a consultant for Alkermes, Inc. and Drug Delivery LLC, and an investigator on a study funded by Alkermes, Inc.

The remaining authors have no conflicts of interest to report.

Availability of data and materials

The sharing of data and materials follows the NIH Data Sharing Policy and Implementation Guidance and the NIH HEAL Public Access and Data Sharing Policy. Final results of the study will be reported in ClinicalTrials.gov, consistent with the requirements of the Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration. Primary data for this study will be available to the public in the NIDA data repository, per NIDA CTN policy. The primary outcome(s) publication will be included

along with the study underlying primary data in the data share repository, and it will also be deposited in PubMed Central per NIH policy.

Abbreviations:

FDA	United States Food and Drug Administration
XR-NTX	extended-release injectable naltrexone
NIH	National Institutes of Health
HEAL	Initiative®, Helping to End Addiction Long-term Initiative
NIDA	National Institute on Drug Abuse
CTN	Clinical Trials Network
SWIFT	Surmounting Withdrawal to Initiate Fast Treatment with Naltrexone
OUD	opioid use disorder
MOUD	medication for opioid use disorder
RP	Rapid Procedure

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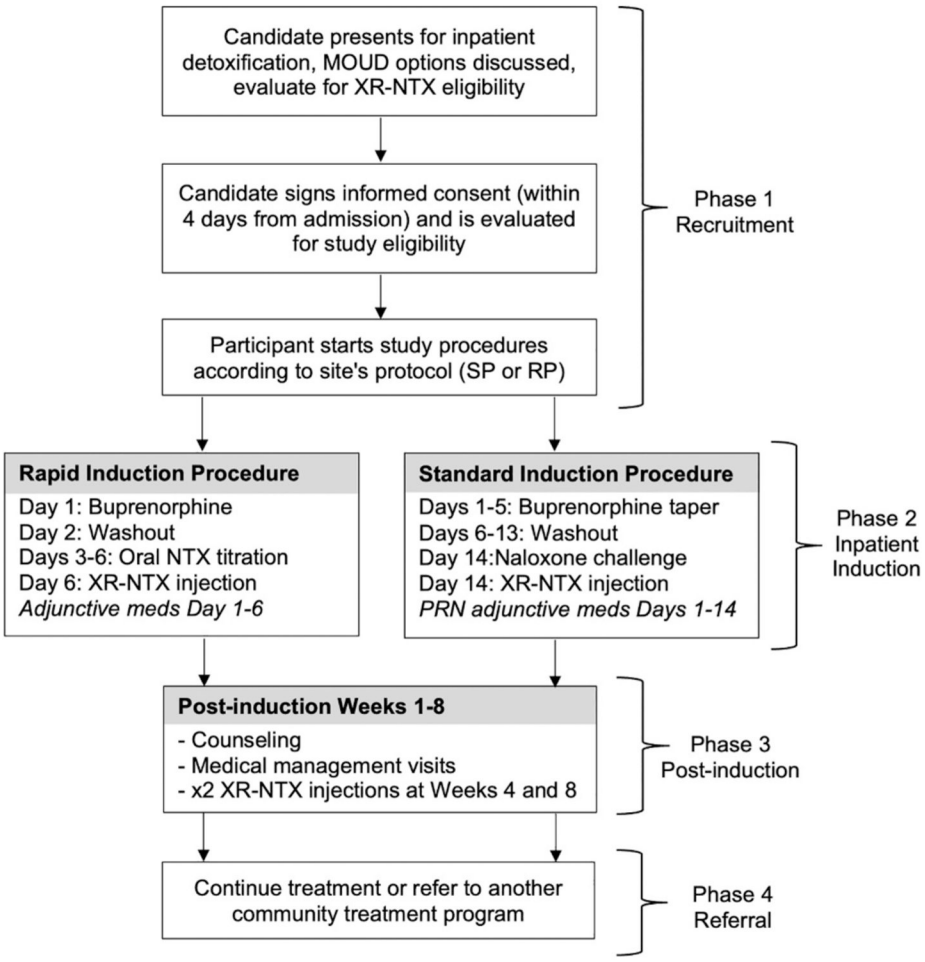
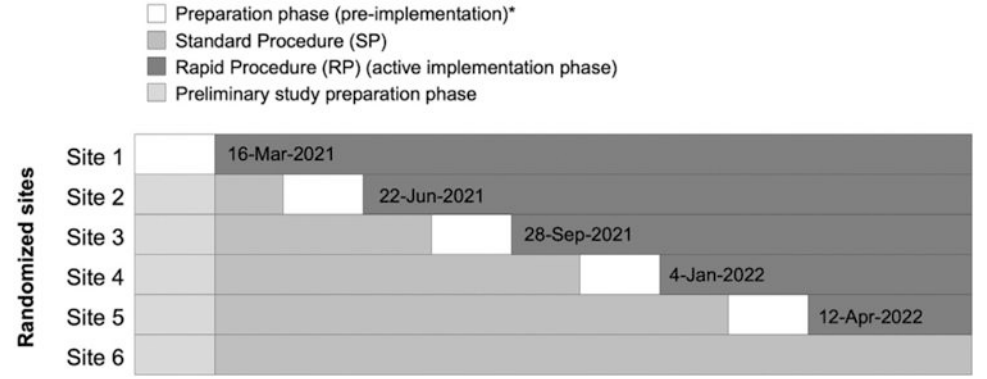


Fig. 1.
Schematic of study phases.

Table 1

Stepped wedge randomization of sites with 8-week preparation (pre-implementation phase) preceding RP active enrollment (implementation phase).



* SP continued through the preparation or pre-implementation phase for Sites 2–5.

Table 2

Standard Procedure (SP) dosing regimen.

Standard Procedure	Buprenorphine	XR-NTX	PRN Adjunctive Medications
Days 1–5	Dosing taper	–	X
Days 6–13	–	–	X
Day 14	–	380 mg IM	X

X = as needed adjunctive medications. Buprenorphine taper dosing varied based on sites' clinical practices. An example buprenorphine taper was 8 mg on Day 1, 6 mg on Day 2, 4 mg on Day 3, 2 mg on Day 4, and 1 mg on Day 5.

Table 3

Rapid Procedure (RP) dosing regimen.

Rapid Procedure	Buprenorphine	1st NTX dose	2nd NTX dose	XR-NTX	Adjunctive Medications
Day 1	2–10 mg	–	–	–	X
Day 2	–	–	–	–	X
Day 3	–	0.5 mg	0.5 mg	–	X
Day 4	–	1 mg	1 mg	–	X
Day 5	–	3 mg	3 mg	–	X
Day 6	–	6 mg	–	380 mg IM	X

X = scheduled adjunctive medications. Scheduled adjunctive medications included: clonidine 0.1–0.2 mg every four hours (with hold parameters for systolic blood pressure < 90 mmHg, or heart rate < 60 beats per minute), clonazepam 1 mg every six hours (with hold for oversedation), antinausea medication daily (prochlorperazine 10 mg or ondansetron 8 mg), sleep aid at bedtime (zolpidem 5–10 mg, trazodone 50–100 mg, or other sleep aids), and nicotine replacement therapy (patch and gum) if tobacco use. Additional doses of adjunctive medications could be given as needed and included antiemetics, sleep aids, and acetaminophen or ibuprofen.

Table 4

Assessment schedule

Assessment	Frequency
General Measures	
Inclusion/exclusion	Screening
Screening log	Throughout study
Locator form	Screening, post-induction weeks 1, 2, 3, 4, 5 or EOM
Demographics form	Consent, baseline
PhenX Tier 1 assessments [60]	Baseline
Prisoner status assessment	Baseline, post-induction Week 3
Motivation scale	Baseline
COVID impact assessment	Baseline
End of induction form	At discharge from inpatient detoxification unit
End of medication treatment form	EOM
Treatment satisfaction survey	Post-induction Week 8
Study completion form	Post-induction Week 8 or if early study termination
Safety and Medical Measures	
Medical and psychiatric history	Screening
HIV and hepatitis assessments	Baseline
Pregnancy and birth control assessment	Screening, before each XR-NTX injection
Fagerström test for nicotine dependence (FTND) [61]	Baseline
NIDA cannabis assessment	Baseline
DSM-5 criteria [20]	Screening
Generalized anxiety disorder (GAD-7) questionnaire [62]	Baseline, repeated weekly through induction phase, post-induction Weeks 1, 2, 3, 4, 5, 6, 8
Patient health questionnaire panic disorder (PHQ-PD) [63]	Baseline
PTSD checklist for DSM-5 (PCL-5) [64]	Baseline
ADHD self-report scale (ASRS) [65]	Baseline
Daily medication administration log	Baseline, daily during induction phase
Concomitant medications	Screening, Post-induction Weeks 1, 2, 3, 4, 6, 8
Adverse events and serious adverse events	Baseline, daily during induction phase, post-induction Weeks 1, 2, 3, 4, 6, 8
Medication injection site abnormality log	As needed throughout study

Assessment	Frequency
Opioid overdose questionnaire	Baseline, post-induction Weeks 1, 2, 3, 4, 6, 8 or EOM
Fatal opioid overdose form	As needed throughout study
Death form	As needed throughout study
Treatment Compliance Measures	
Critical action checklist for RP/SP	Weekly during induction phase
Medical management log	At each study visit
Psychosocial participation log	At each study visit
Outcome Measures	
Timeline Followback (TLFB) for substance use [66]	Baseline, post-induction Weeks 1, 2, 3, 4, 6, 8
Timeline Followback (TLFB) for MOUD	Baseline, post-induction Weeks 1, 2, 3, 4, 6, 8
Urine drug screen (UDS) (with fentanyl testing)	Screening, before each XR-NTX injection
Clinical opiate withdrawal scale (COWS) [67]	Baseline, daily or more frequently (depending on RP or SP) during induction phase
Subjective opioid withdrawal scale (SOWS) [68]	Baseline, daily during induction phase, post-induction Weeks 1, 2, 3, 4, 6, 8
Visual analog scales (VAS) opioid craving	Baseline, daily during induction phase, post-induction Weeks 1, 2, 3, 4, 6, 8
Visual analog scales (VAS) opioid response	As needed throughout post-induction phase
Patient health questionnaire for depression (PHQ-9) [69]	Baseline, weekly during induction phase, post-induction Weeks 1, 2, 3, 5, 6, 8
Mental health assessment (for suicidality)	As needed throughout the study
Health Services Measures	
Patient-reported outcomes measurement information (PROMIS) [70]	Baseline, post-induction Weeks 4, 8
Non-medical and other services (NMS) [71,72]	Baseline, post-induction Weeks 4, 8
Genetics Measures	
Genetics sample	Baseline
Family origin assessment	Baseline
Implementation Process Measures	
Organizational level clinical implementation data collection form	Every 14 weeks
Individual staff readiness and preparedness rulers	Before RP training in 8-week pre-implementation phase and after 14-week step
Organizational readiness to change assessment (ORCA)	Before RP training in 8-week pre-implementation phase and after 14-week step
Organizational fidelity to pre-implementation checklist	After 8-week RP pre-implementation phase
Organizational fidelity to implementation checklist	After 14-week step of RP implementation
Site needs qualitative assessment	At start of 8-week RP pre-implementation phase
Site implementation process qualitative notes	Frequency varied based on site-level implementation

Assessment	Frequency
Individual staff semi-structured qualitative interviews	After 14-week step of RP implementation

Abbreviations: RP = rapid induction procedure; SP = standard induction procedure; EOM = end of medication; XR-NTX = extended-release injectable naltrexone; NIDA = National Institute on Drug Abuse; DSM-5 = diagnostic and statistical manual of mental disorders fifth edition; PTSD = post-traumatic stress disorder; ADHD = attention deficit hyperactivity disorder; MOUD = medications for opioid use disorder.

Table 5

Implementation outcomes by RE-AIM category.

Domain	Data Source/Assessment
Reach	
# of screen failures and reasons	Screening log
# of OUD patients admitted and % enrolled in RP	Organizational level clinical implementation data collection
# of RP participants and % induction failures (include patient characteristics)	End of induction form
Effectiveness	
# and % of patients successfully inducted onto XR-NTX by RP (include patient characteristics)	Organization level clinical implementation data collection
# of days from admission to XR-NTX	Electronic medical record
Fidelity to key RP components	Critical action checklist
Opioid withdrawal symptoms during RP	COWS and SOWS
Opioid cravings during RP	VAS
Adverse effects for RP	Adverse and serious adverse events form
Patient experience and treatment satisfaction	End of induction form and treatment satisfaction survey
Adoption	
# and % of staff (include characteristics) reporting readiness and preparedness (before and after 14-week step of implementation)	ORCA and readiness/preparedness rulers
Qualitative assessment of staffs perspectives and experience	Semi-structured staff interviews
Implementation	
Staff (include characteristics) report on knowledge of intervention and implementation climate (before and after 14-week step of implementation)	ORCA
# of clinicians on site-level implementation team	Fidelity to pre-implementation checklist
# of non-clinical administrative leaders on site implementation team	Fidelity to pre-implementation checklist
# and % of staff in attendance at RP trainings	Fidelity to pre-implementation checklist
Hours of clinical consultation received per site	Meeting time logs
Average rate of adherence to core components of RP	Critical Action Checklist
Qualitative assessment of barriers and facilitators influencing implementation	Semi-structured staff interviews and implementation process notes
Maintenance	
Qualitative assessment of factors influencing maintenance and sustainability	Semi-structured staff interviews and implementation process notes

Abbreviations: RP = rapid induction procedure; XR-NTX = extended-release injectable naltrexone; COWS = clinical opiate withdrawal scale; SOWS = subjective opiate withdrawal scale; ORCA = organizational readiness to change assessment.