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# Extended-release naltrexone to prevent relapse among opioid dependent, criminal justice system involved adults: Rationale and design of a randomized controlled effectiveness trial

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ABSTRACT

*Background:* Extended-release naltrexone (XR-NTX, Vivitrol®; Alkermes Inc.) is an injectable monthly sustained-release mu opioid receptor antagonist. XR-NTX is a potentially effective intervention for opioid use disorders and as relapse prevention among criminal justice system (CJS) populations.
*Methods:* This 5-site open-label randomized controlled effectiveness trial examines whether XR-NTX reduces opioid relapse compared with treatment as usual (TAU) among community dwelling, non-incarcerated volunteers with current or recent CJS involvement. The XR-NTX arm receives 6 monthly XR-NTX injections at Medical Management visits; the TAU group receives referrals to available community treatment options. Assessments occur every 2 weeks during a 24-week treatment phase and at 12- and 18-month follow-ups. The primary outcome is a relapse event, defined as either self-report or urine toxicology evidence of ≥10 days of opioid use in a 28-day (4 week) period, with a positive or missing urine test counted as 5 days of opioid use.
*Results:* We describe the rationale, specific aims, and design of the study. Alternative design considerations and extensive secondary aims and outcomes are discussed.
*Conclusions:* XR-NTX is a potentially important treatment and relapse prevention option among persons with opioid dependence and CJS involvement.
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## 1. Introduction and background

Opioid dependence and opioid use disorders are common in the criminal justice system (CJS). Arrested individuals tested positive for opiates at rates of 5–20% in the 2013 US Arrestee Drug Abuse Monitoring Program II [1]. Evidence-based treatments including methadone and buprenorphine are usually

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unavailable during incarceration [2,3], and rates of opioid relapse and overdose death are elevated at release [4]. While these medication assisted treatment modalities are associated with improved outcomes [5–11], community supervision (i.e., parole, probation) authorities typically discourage their use [12]. In addition, well-known stigmas and prior negative treatment experiences may bias affected individuals from pursuing these medications [2,13,14].

Extended-release (XR-NTX), or sustained-release injectable naltrexone, is a long-acting medication that was approved for the treatment of opioid dependence by the US Food and Drug Administration (FDA) in 2010. XR-NTX may be particularly beneficial to criminal justice system (CJS) and opioid-involved populations. These typically emerge from incarceration 'drug free' and no longer physically dependent, lack ready access to agonist treatments, and are at high risk for relapse. Psychosocial treatment adherence, opioid-free urines, and frequent monitoring are often mandated by CJS authorities. Naltrexone, meanwhile, is not a controlled substance and requires pre-induction detoxification to a 'drug free' state. For these reasons, XR-NTX may be more readily acceptable and adaptable in CJS and other traditionally 'drug free' treatment settings. Naltrexone is not a controlled substance and requires an active user detoxify prior to induction. For these myriad reasons, XR-NTX may be more readily acceptable and adaptable in CJS and other traditionally 'drug free' opioid treatment settings [15].

XR-NTX's sustained-release technology provides gradual release of sufficient naltrexone to block the mu opioid receptor agonist effects of up to 25 mg of intravenous heroin or an equivalent amount of other opioids for at least one month after injection [16,17]. In an initial 2-site US randomized placebo-controlled trial, an alternative extended-release naltrexone formulation (Depotrex) was effective at preventing relapse after detoxification among community-recruited heroin users [18]. Treatment retention was 68% after 2 months and opioid use outcomes were superior vs. placebo. A large double-blind placebo-controlled randomized trial conducted in Russia established XR-NTX's superiority over placebo in preventing opioid use and relapse following an inpatient detoxification induction among a general adult opioid (heroin) dependent population, and was the pivotal trial leading to FDA approval [19]. However, further US community and criminal justice system effectiveness trials of XR-NTX opioid treatment, including this protocol, are only now underway (NCT01180647, NCT01246401, NCT02032433, NCT01999946, and NCT02110264).

A preceding single-arm observational cohort study conducted by this trial's 5-site consortium demonstrated the feasibility of inducting community-dwelling parolees and probationers onto XR-NTX (Depotrex) [20]. Participants remaining on XR-NTX for up to 6 months had lower rates of opioid use vs. earlier treatment drop outs. This earlier pilot experience greatly informed the conception and implementation of this current randomized effectiveness trial.

## 2. Research design and study population

### 2.1. Study design

This is a 5-site open-label, unblinded randomized effectiveness trial that compares 24 weeks of XR-NTX treatment vs. Treatment-as-Usual (TAU) among community-dwelling CJS-involved participants with a history of opioid dependence. The effectiveness trial design intends to estimate the benefit of XR-NTX under real world conditions.

### 2.2. Research questions and hypotheses

The principal research question is whether assignment of a CJS- and opioid-involved population to the XR-NTX treatment arm reduces the likelihood of an opioid relapse event, and, more generally, of overall rates of opioid use (i.e., % days of use, proportions of urines positive). We hypothesize that XR-NTX treatment assignment will be associated with a significantly lower likelihood of an opioid relapse event, longer relapse-free survival, and lower overall rates of opioid use (i.e., more opioid-free weeks).

Alongside this hypothesized primary treatment effect on opioid addictions are secondary outcomes, including potential beneficial effects of XR-NTX treatment assignment on rates of HIV risk behaviors, including intravenous (IV) drug use and unsafe sex, heavy alcohol use and non-opioid other drug misuse (i.e. cocaine), continued criminal activities, re-arrest, and re-incarceration, health and social costs, and safety events, including overdose and mortality. We hypothesize that XR-NTX treatment assignment will be associated with significantly lower rates of alcohol and non-opioid drug misuse, HIV risk behaviors, re-arrests and re-incarcerations, lower costs to the extent that XR-NTX treatment will be cost-effective, and lower rates of opioid overdose.

We are also interested in the extent to which CJS-involved participants report feeling coerced or mandated into study participation, given an overall historic bias on the part of CJS authorities against agonist medications and preferences favoring 'drug free' recovery. Though participation in this study is voluntary and referrals from CJS authorities are not accepted, we will assess the degree to which participants perceive their decision to participate in the study was coerced or voluntary.

### 2.3. Study organization and sites

Five independently funded centers are implementing a common protocol under an NIH collaborative clinical trial R01 mechanism (PAR-07-232). The lead site, the University of Pennsylvania (Philadelphia, PA), hosts the regulatory, data management, and statistical cores. The four remaining sites are New York School of Medicine and Bellevue Hospital Center (New York, NY), Brown University and Rhode Island Hospital (Providence, RI), Columbia University (NY, NY), and Friends Research Institute (Baltimore, MD).

### 2.4. Study population and inclusion/exclusion criteria

Eligible subjects are community-dwelling adults with criminal justice system involvement and a history of opioid dependence. Inclusion/exclusion criteria were designed to assemble a representative sample of CJS opioid dependent adults, including those with significant medical and psychiatric co-morbidities, provided that study participation appears safe. Persons excluded are currently on or seeking methadone or buprenorphine treatment by self-report, which are relative contraindications to naltrexone, females