Naltrexone Enhanced Addiction Treatment (NEAT)

A randomised controlled trial of the clinical and cost-effectiveness of

extended-release naltrexone and oral naltrexone

CLINICAL STUDY PROTOCOL V(6.0)

Trial Identifiers

EudraCT Number:	2013-002584-25
ISRCTN:	ISRCTN95809946
REC Number:	REC 14/LO/1615
HTA project no	10/46/01

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1. Study Synopsis

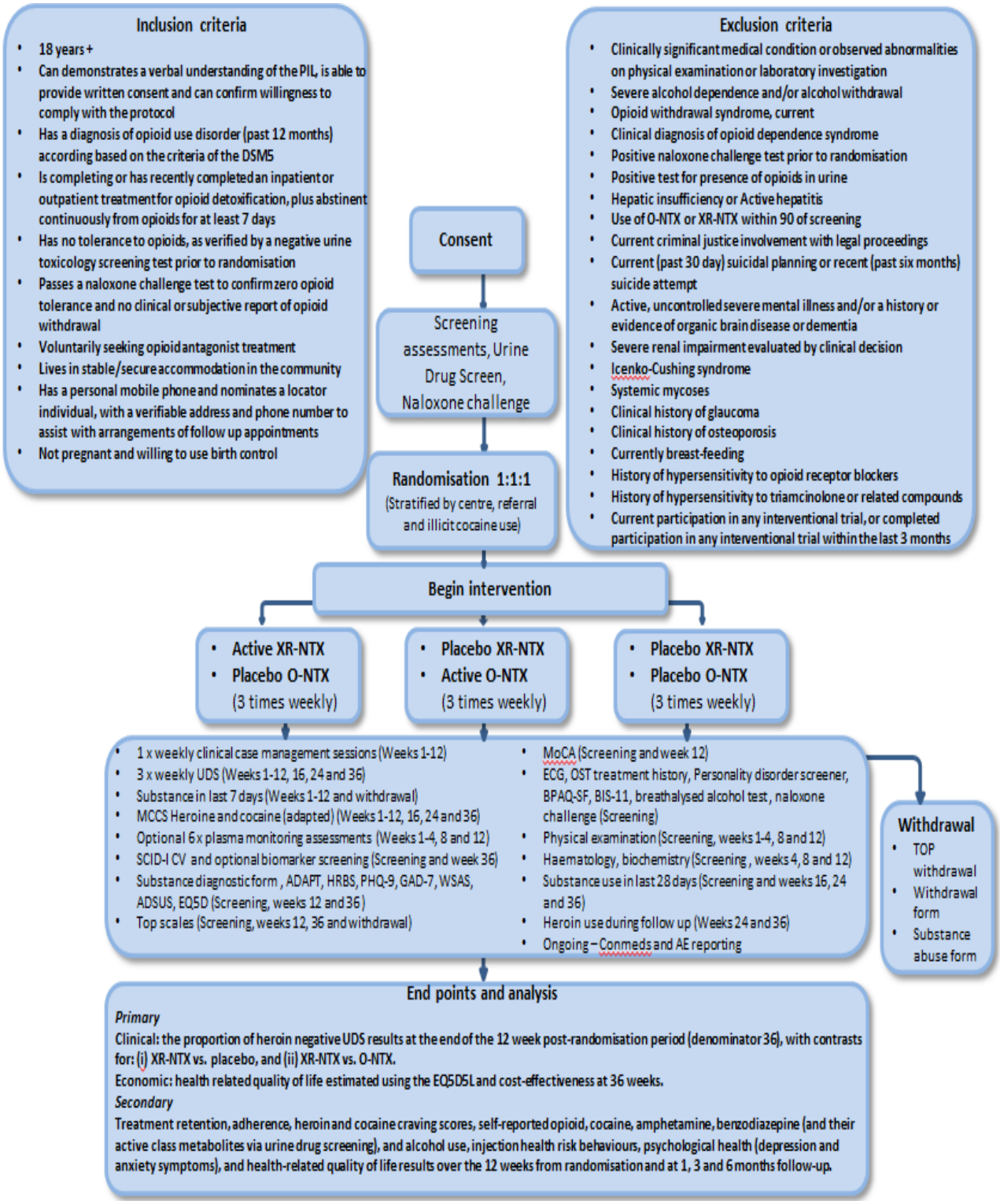
Title Of Clinical Trial:	A randomised controlled trial of the clinical and cost-effectiveness of extended-release naltrexone and oral naltrexone
Protocol Short Title/ Acronym:	Naltrexone Enhanced Addiction Treatment trial (NEAT)
Study Phase If Not Mentioned In Title:	Phase III clinical trial of an investigational medicinal product
Purpose Of Clinical Trial:	The NEAT trial is for adults with a diagnosis of opioid use disorder (DSM5) in the past year, who are now detoxified (zero opioid tolerance) and want help to stay away from heroin. The primary purpose of the trial is to evaluate the clinical and cost-effectiveness of enhanced naltrexone (NTX) relapse prevention therapy programme for the treatment of opioid use disorder (following NICE, 2007). The NEAT trial will evaluate two formulations of this medication: a 90-day implanted, long-acting form (XR-NTX; 'iGen/Atral-Cipan' device herein), and a short-acting oral tablet form (O-NTX, the active comparator).
Primary Objective:	A. Is XR-NTX treatment more effective than placebo at reducing heroin use? B. Is XR-NTX more effective than O-NTX at reducing heroin use? C. Is XR-NTX more cost- effective than placebo in terms of quality-adjusted life years? D. Is XR-NTX more cost-effective than O-NTX in terms of quality-adjusted life year?
Secondary Objectives:	A. To compare treatment retention and medication and psychological intervention adherence rates among the XR-NTX, O-NTX and placebo conditions. B. To contrast the XR-NTX, O-NTX and placebo conditions on quality of life indices. C. To contrast XR-NTX, O-NTX and placebo conditions on: • heroin and cocaine craving; • self-reported opioid, cocaine, amphetamine and benzodiazepine use (with past 48 hour abstinence verified via urine drug screening [UDS]); • alcohol use; • injection health risk behaviours; • psychological health (depression and anxiety symptoms); • molecular (genetic) biomarkers of treatment response. • Plasma naltrexone and 6-β-naltrexol (the primary metabolite of NTX); D. To document the safety of XR-NTX and O-NTX. E. To compare patterns of heroin relapse among the XR-NTX, O-NTX and placebo conditions
Trial Design:	A three-year definitive, three-centre, three-arm, parallel group, placebo controlled, double-blind, double-dummy, randomised clinical trial, with primary outcomes assessed 12 weeks after randomisation, and with clinic

	conducted research follow-ups staged at 16, 24 and 36 weeks.
Clinical settings:	Two specialist NHS outpatient addiction clinics in London and Birmingham.
Primary Endpoints:	Clinical: the proportion of heroin negative UDS results at the end of the 12 week post-randomisation period (denominator 36), with contrasts for: (i)XR-NTX vs. placebo, and (ii) XR-NTX vs. O-NTX. Economic: health related quality of life and cost-effectiveness at 36 weeks with comparisons for (i) XR-NTX vs. placebo, and (ii) XR-NTX vs, O-NTX.
Sample Size:	300 adult patients
Imp, Dosage And Route Of Administration:	1 iGen/Atral-Cipan XR-NTX device (765mg naltrexone or Placebo) at Day 0 of Study Week 1. 3 x weekly directly observed (clinic supervised) active or placebo O-NTX tablets (2 x 50mg, Monday and Wednesday; 3 x 50mg, Friday) at Day 0 of Study Week 1 (for 4 weeks) and then an 8 week regimen of patient administered dosing at the same dosing level contingent on return of medication packaging and reports of dosing. (NB: The higher dose given on Fridays provides extended therapeutic coverage for the patient because the clinic is closed at the weekend).
Estimated time line	Project start: September 2014 First patient in: March 2015 Last patient out: December 2017 Project end: May 2018
Protocol status (draft/ final)	Final
Version And Date Of Final Protocol:	3.0 (27.07.15)
Version And Date Of Protocol Amendments:	2.0 (26.09.14) 1.11 (13.08.14)

2. Glossary of terms

Abbreviation	Definition
AE	Adverse Event
AR	Adverse Reaction
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
ISRCTN	International Standardised Randomised Controlled Trial Number
MHRA	Medicines & Healthcare products Regulatory Agency
KCTU	King's Clinical Trials Unit, King's College London
KHP-CTO	King's Health Partners Clinical Trials Office
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NTX	Naltrexone
O-NTX	Naltrexone (oral tablet)
XR-NTX	Naltrexone (extended release implant)
OST	Opioid Substitution Therapy
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPC / SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UDS	Urine Drug Screen

3. Contents



4. Trial Summary

What is the clinical and cost-effectiveness of enhanced naltrexone (NTX) in the treatment of opioid use disorder? The Naltrexone Enhanced Addiction Treatment for Opioid Use Disorder Trial (NEAT), is the first phase III UK study to coalesce anatagonist medication and behavioural interventions for the treatment of this population.

The study will be implemented in two specialist NHS outpatient addiction clinics in London and Birmingham. (recruitment centres), each with formal links for research trials with a local University.

Three hundred recently detoxified, formerly dependent heroin users will be randomised to one of three conditions to receive on-site supervised:

- thrice-weekly oral active NTX tablets plus placebo extended-release NTX at the start of treatment; or
- oral placebo plus active extended-release NTX; or
- oral placebo NTX plus placebo extended-release NTX.

Each condition will be delivered over 12 weeks. All participants will receive standard NHS psychological interventions (weekly individual counselling) and a behavioural protocol incentivising clinic attendance to receive trial medication and complete research assessments.

The primary outcome measure is the number of heroin negative urine screening (UDS) tests in treatment (taken thrice weekly during the 12 week treatment phase of the trial; 36 UDS tests in total). In addition to societal focused health-related cost-effectiveness, secondary objectives relate to treatment retention/adherence, craving for heroin and cocaine and monitoring of naltrexone and 6-β-naltrexol (the primary metabolite of NTX). Research worker administered follow-up assessments will be at 16, 24 and 36 weeks after the active 12 week treatment phase.

5. Background & Rationale

The term ‘opioids’ refers to semi-synthetic and synthetic analgesic compounds with similar properties to the group of psychoactive analgesic substances derived from the poppy plant, including opium, morphine and codeine. In England, ‘street’ heroin is the most harmful illegal opioid in the UK[i]. Illicit heroin makes the user feel intense euphoria. It has an aggressive dependence liability, the predominant symptom being compulsive drug use, despite significant health and social harms[ii]. Physiologically dependent users need to take heroin every day to avoid the onset of acutely unpleasant, flu-like, withdrawal symptoms. Users report experiencing intense feelings of wanting and needing to take heroin and find it very difficult to stop. Craving is considered to be a core symptom of addiction and a prime cause of relapse[iii]. Untreated, opioid dependence is a persistent and debilitating condition, associated with the majority of social costs arising from drug misuse. The lives of most heroin addicts are multiple disadvantaged and there is a strong link between heroin and acquisitive crime. There is also an associated major public health burden with the acquisition and transmission of blood borne viral infections. Consequently, tackling the problem of opioid dependence is a high priority for the Government and the NHS.

The majority of individuals presenting to specialist NHS community treatment clinics have established harmful illicit opioid use disorder, almost all related to street heroin. However, the addition of cocaine dependence adds considerable severity to the individual case and this patient sub-group has a relatively poorer outcome compared to primary heroin users[iv]. In 2008/09 there were 321,229 individuals in England with problems relating to heroin and/or crack cocaine (corresponding to 9.4 per thousand of the population aged 15-64[v]). In 2008/09 combined use of heroin and cocaine was reported in 29% of patients admitted for treatment[vi]. Intravenous injection is the preferred route of administration by approximately one-third of heroin users, with associated risks of infection and overdose. There are also substantially elevated rates of mood disorders among heroin users compared to the general population[vii], and after opioid detoxification, in addition to craving for heroin, patients often report a syndrome of anhedonia including affective disorders (depression, dysphoria and anxiety). These symptoms may trigger recurrence in heroin use[viii].

The chronic relapsing nature of drug dependence means that helping a patient achieve stable abstinence is often difficult. In the NHS, the front-line clinical response to heroin dependence is the prescription of a substitute (full or partial) μ-opioid agonist (oral methadone, oral buprenorphine hydrochloride, or oral buprenorphine-naloxone medication) taken once daily in the context of case management and general counselling support. If the patient receives an appropriate prescribed dose of opioid agonist maintenance therapy, physiological tolerance to opioids is medically managed and there are usually no breakthrough withdrawal symptoms before next dosing. OST medication is administered directly under clinical supervision or by the patient at home.

Properly delivered OST creates a platform for patients to receive structured psychosocial interventions. All patients are supported by a keyworker and may also receive structured psychosocial treatment if needed. A specified keyworker (a physician, psychologist, or more commonly a nurse, social worker or trained non-medical drugs worker) takes the lead role in coordinating a patient's care. Through regular clinic appointments, the keyworker gives practical advice, applies psychological techniques to build motivation to reduce drug-related harms and organises access to community services as required. In around two-thirds of patients receiving substitution treatment, the prescribing physician maintains the patient on a stable daily dose for as long as is clinically indicated, and then supervises a gradual withdrawal to achieve opioid abstinence. In the remainder of cases, prescribing is of shorter duration, usually involving a gradual withdrawal of medication immediately following stabilisation.

However, not all patients derive a clinical benefit from OST. Some respond initially, then lapse to resumed heroin use during treatment; a minority deteriorate progressively during treatment; some patients and clinicians prefer abstinence, rather than a maintenance approach from the outset; and some patients prefer to continue their personal recovery journey by withdrawing early from agonist therapy and receiving support for abstinence. Overall, reduced therapeutic engagement, ongoing or resumed street heroin and cocaine or amphetamine use, and variations in satisfaction with medication vary widely between programmes. Furthermore, some patients do not wish to receive OST. The chronic relapsing nature of drug dependence means that helping a patient achieve stable abstinence is often difficult. There are substantially elevated rates of mood disorders among heroin users compared to the general population[ix], and after opioid detoxification, in addition to craving for heroin, patients often report a syndrome of anhedonia including affective disorders (depression, dysphoria and anxiety). These symptoms may trigger recurrence in heroin use[x]. Unfortunately psychological supports have been shown to be not particularly effective at helping patients to maintain abstinence and the NHS currently has no significant alternative treatment options.

The NEAT trial addresses this need and evaluates an *μ*-opioid antagonist called naltrexone (NTX) as part of a relapse prevention maintenance programme for formerly opioid dependent individuals who are seeking abstinence treatment. Naltrexone blocks the effects of any subsequently ingested heroin and prevents physical dependence. Naltrexone is used as a treatment for alcohol dependence by reducing craving for alcohol and the subjective reinforcement effects of drinking[xi]. For opioid dependence, naltrexone does not directly reduce craving for heroin; but in the absence of the physical effects of heroin, clinical studies of maintenance therapy indicate that craving gradually attenuates[xii]. This highlights the importance of combining NTX with behavioural therapies to maintain abstinence.

NTX is rapidly absorbed, metabolised by the liver and excreted in the urine with an elimination half-life of four hours (13 hours for the principal metabolite 6-β-naltrexol). Behaviourally, NTX blocks the euphoric effects of opioids. It has no psychoactive effect of its own, and tolerance and dependence do not develop[xiii]. Clinical studies indicate that 50mg of oral tablet naltrexone hydrochloride (O-NTX) will block the pharmacological effects of 25mg of intravenously administered heroin for a period of at least 24 hours. Doubling this dose provides blockade for around 48 hours, and tripling the dose provides pharmacological opioid blockade for approximately 72 hours. Depending on whether one, two or three days elapse before a patient's next clinic visit to receive medication, a dose of 50mg, 100mg, or 150mg is prescribed. An open-ended and flexible approach to the dosing regimen and the duration of treatment is usually used in routine NHS practice with this medication. Patients may receive 50mg of O-NTX each weekday with a 100mg dose on Saturday, or patients may receive 100mg every other day, or 150mg every third day. Several clinical trials have used the

following dosing regimen: 100mg on Monday; 100mg on Wednesday; and 150mg on Friday. This schedule is acceptable to patients, balances the level of attendance at the clinic required to collect research assessments, and will, therefore, be used in our study.

O-NTX has an excellent pharmacological profile as an opioid blocker. However, as a relapse prevention pharmacotherapy it has produced disappointing results. The main reason for this is that patients who succumb to cravings (or are otherwise motivated to use heroin) can relatively easily discontinue their medication and then return to heroin use. Consequently, retention has been shown to be poor in all but the most motivated or socially supported patients. There have been several meta-analyses. In 2006, Berglund and colleagues reported on 10 studies of O-NTX versus control (seven placebo), and six studies of psychosocial/psychopharmacological interventions involving 1,071 patients randomized to oral NTX maintenance therapy for opioid use disorder or a control[xiv]. This review pointed to retention as the key variable in explaining NTX's effectiveness. The studies with the highest retention in the experimental group had better results than the control group for differences in retention, opioid-positive urines, psychiatric symptoms and craving for heroin during the experimental period. Among these were those studies which incentivized clinic attendance for each dose by offering vouchers which could be exchanged for recovery appropriate goods or services. In these trials, there was increased retention and a greater reduction in the number of opioid-positive urines[xv].

In 2007, for a Health Technology Assessment for NIHR[xvi], Adi and colleagues reported on 26 studies with 940 participants. They concluded that the methodological quality of the reviewed trials was poor to moderate. Results suggested that O-NTX may be better than placebo in terms of retention in treatment, but overall this was not statistically significant. Among the trials including a contingency management element, the mean length of time patients stayed on NTX was 7.4 weeks, compared with 2.3 to 5.6 weeks on NTX treatment alone. Nevertheless, on the basis of the evidence and clinical experience, NICE recommends that "naltrexone is recommended as a treatment option in detoxified formerly opioid-dependent people who are highly motivated to remain in an abstinence programme"[xvii].

Against the background of clinical evidence for O-NTX, there is a clear logic for a sustained release formulation of NTX: it removes the need for the patient to remember to take the medication (usually either daily or thrice weekly). Medical products variously described by prefix as controlled, modified, slow, extended, sustained, or prolonged-release (extended-release [XR] is the term used herein) are designed to reduce the frequency of dosing by modifying the rate of release and absorption of an active substance. Such products have been available for some time and used effectively to treat a wide range of clinical indications. First generation products achieved modified-release through intramuscular or subcutaneous injections of suspensions of insoluble drug complexes.

The development of XR-NTX formulations has renewed interest in this medication for treating opioid use disorder. There are two formulations of XR-NTX in active production. Vivitrol® (Alkermes Waltham, MA) is an injectable depot product, approved and licensed by the USA Food and Drug Administration to treat opioid and alcohol use disorder. Prodetoxon is a dissolution-control implanted product, licensed in Russia (Fidelity Capital, Moscow). Injected XR-NTX has been used successfully in research studies[xviii,xix]. The Comer and colleagues' study has been used for the NEAT sample size calculations. In Norway, the Kunøe study involved 56 detoxified formerly opioid dependent patients voluntarily seeking relapse prevention therapy. They were randomized to receive either an unlicensed XR-NTX implant device (GoMedical Industries) or non-standardised aftercare over six months. XR-NTX patients had on average 60 days less opioid use than controls across the follow-up period ($P<0.05$). For Vivitrol and Prodetoxon, clinical reports point to good patient acceptability and effectiveness. They have been in routine clinical use at the St. Petersburg Addiction Clinic for the past decade[xx]. Encouraging interim results of a randomized controlled trial of Prodetoxon have been reported[xxi], with full results forthcoming (Krupitsky, personal communication).

In the NEAT trial, initial approaches to the manufacturers to discuss access to both Prodetoxon and Vivitrol for the study proved unsuccessful. Alkermes declined to donate supplies and were not willing to supply a

placebo and commercial purchase costs were not supported by the NHS. Fidelity Capital were unable to facilitate QP inspection of their manufacturing facility.

During this process, a new implant has been in development based on a 90-day implant technology (with similarities to Prodetoxon). This product (the iGen/Atral-Cipan device) is manufactured in the European Union (the only XR-NTX product to be made in the EU) and is now imported for use in the UK on a special medication/named patient basis. The iGen/Atral-Cipan device (NTX: 765mg) is inserted subcutaneously during a simple surgical procedure into the abdominal wall by a pre-filled syringe insertion device, via a 1.5cm incision under local anaesthetic, with blunt dissection and incision closure using an absorbable suture. The manufacturer has agreed to donate supplies of active implant medication to the study.

6. Trial design and objectives

6.1 Trial Design

NEAT is a three year definitive, two-centre, three-arm, parallel group, placebo controlled, double-blind, double-dummy, phase III randomised clinical trial. It evaluates and compares the effectiveness of O-NTX with implanted XR-NTX as relapse prevention therapy for opioid use disorder. After a literature review and discussion with experts, we selected 12 weeks as an optimum duration over which to deliver medication and the psychological intervention and the incentivized clinical attendance protocol. Primary and secondary outcomes will be assessed after 12 weeks, with follow-up interviews after 16, 24 and 36 weeks

The trial will be double blind. Active and placebo oral medication will be produced and encapsulated identically. Active and placebo implant devices will be produced and packaged identically. Clinicians and research workers completing baseline, clinic attendance assessments and all follow-ups will be blind to group allocation, as will patients and pharmacists. This design will ensure that the study has a high level of both treatment integrity (delivery of the treatment as intended) and treatment differentiation (treatment conditions differed from one another in the intended manner). The trial has three groups:

- Group A: Active XR-NTX and placebo O-NTX
- Group B: Placebo XR-NTX and active O-NTX
- Group C: Placebo XR-NTX and placebo O-NTX

6.2 Trial objectives and endpoints

The NEAT trial is for adults who have been diagnosed with opioid use disorder (DSM5) in the past year, but are now detoxified (zero opioid tolerance) and are voluntarily seeking help to stay away from heroin. Our study will test whether NTX is effective in helping formerly opioid dependent patients to maintain abstinence from heroin. We will look at two formulations of this medication: an implanted, long-acting (90 day) form (XR-NTX; iGen/Atral-Cipan device), and a relatively short-acting oral tablet form (O-NTX, the active comparator). NEAT will determine whether XR-NTX is more effective than placebo (placebo oral tablet NTX and placebo implant) at maintaining heroin abstinence, and also whether XR-NTX is more effective than O-NTX.

There will be two measures of effectiveness: clinical (heroin abstinence) and economic (quality of life adjusted life years) to be combined with a broad concept of resource use and costs. The economic assessment is particularly important because although XR-NTX is currently much more expensive than O-NTX, it may prove to be much more effective and potentially cost saving in relation to other treatments and/or criminal justice sector costs.

6.2.1 Primary objective

A. Is XR-NTX treatment more effective than placebo at reducing heroin use?

B. Is XR-NTX more effective than O-NTX at reducing heroin use?

C. Is XR-NTX more cost-effective than placebo in terms of quality-adjusted life years?

D. Is XR-NTX more cost-effective than O-NTX in terms of quality-adjusted life year?

NB: Objectives A and B are assessed by UDS verified abstinence from heroin.
NB: Objectives C and D are assessed using health-related quality of life

6.2.2 Secondary objective

A. To compare treatment retention and medication and psychological intervention adherence rates among the XR-NTX, O-NTX and placebo conditions.
B. To contrast the XR-NTX, O-NTX and placebo conditions on Quality of Life indices
C. To contrast XR-NTX, O-NTX and placebo conditions on heroin and cocaine craving, self-reported opioid, cocaine, amphetamine and benzodioazepine use (abstinence verified by UDS), alcohol use, injection health risk behaviours, psychological health (depression and anxiety symptoms); molecular (genetic) biomarkers of treatment response and levels of plasma naltrexone and 6-β-naltrexol (the primary metabolite of NTX);
D. To document the safety of XR-NTX and O-NTX
E. To compare patterns of heroin relapse among the XR-NTX, O-NTX and placebo conditions

6.2.3 Primary endpoints

Clinical: the proportion of heroin negative urines at the end of the 12 week post-randomisation period (denominator 36), with contrasts for: (i) XR-NTX vs. placebo, and (ii) XR-NTX vs. O-NTX.

Economic: health related quality of life and cost-effectiveness at 36 weeks.

6.2.4 Secondary endpoints

Treatment retention, adherence, heroin and cocaine craving scores, self-reported opioid, cocaine, benzodiazepine (and their active class metabolites via urine drug screening), and alcohol use, injection health risk behaviours, psychological health (depression and anxiety symptoms), and health-related quality of life results over the 12 weeks from randomisation and at 16, 24 and 36 week follow-up.

6.3 Trial time line

	Screening period[1]	Study week													Follow-up					
Measure	**-2-0**	**R**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16**	**24**	**36**	Ongoing	Withdrawal	Relapse
Consent & Registration form	X																			
Eligibility	X																			
Randomisation form		X																		
Medical history	X																			
Vital signs	X		X	X	X	X				X				X						
ECG form	X																			
OST treatment history section	X																			
Haematology & Biochemistry[2]	X					X				X				X						
Plasma monitoring			X	X	X	X				X				X						
Biomarker Screening (optional)	X																X			
Implant form			X																	
Dosage check																		X		
Implant check[3]			X	X	X	X	X	X	X	X	X	X	X	X						
Urine drug screen[4]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Naloxone challenge	X																			
Adapted SCID-5 RV (Mood episodes, Anxiety and other disorders)	X																X			
Substance use diagnostic form	X													X			X			
Personality Disorder Screener	X																			
BPAQ-SF	X																			
BIS-11	X																			
ADAPT	X													X			X			
MoCA	X													X						
HRBS	X													X			X			
Substance use in last 7 days[4]			X	X	X	X	X	X	X	X	X	X	X	X					X	
TOP-SCALES	X													X			X		X	
MCCS (adapted)[5]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
MCCS for heroin[5]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
PHQ-9	X													X			X			
GAD-7	X													X			X			
WSAS	X													X			X			
ADSUS	X													X			X			
EQ5D	X													X			X			
First heroin lapse																				X
Therapy sessions			X	X	X	X	X	X	X	X	X	X	X	X						
Patient treatment guess																	X			
Clinician treatment guess																	X			
AE form																		X		
Conmeds																		X		

Incentivised voucher protocol[3]			X	X	X	X	X	X	X	X	X	X	X	X						
Withdrawal form																			X	
Patient status at 12 weeks														X						
Patient status at 16 weeks															X					
Patient status at 24 weeks																X				
Patient status at 36 weeks																	X			
Adapted 28 day Substance use	X														X	X	X			
Heroin use during follow up																X	X			

[a]Screening period will last a maximum of 2 weeks

[2]Historical haematology & biochemistry test up to 2 months old can be used

[3]Taken 3 times weekly until week 12

[4]Taken 3 times weekly until week 12, then once for the follow up visits

[5]Measures to be taken on the last visit of the week

*Unless specified, all measures will be taken on the first visit of the week. When a patient misses the first visit of the week, the next visit will be used.

6.4 Investigational Medicinal Products

NTX is a synthetic congener of oxymorphone with no opioid agonist properties. It is a long acting, non-selective, competitive antagonist with the highest affinity at μ-opioid receptors.

The study team will apply for a EudraCT number and prepare and submit the CTA application, along with the Investigational Medicinal Product dossiers for the oral and implantable medications and their matching placebos, via the KHP-CTO. Substantial amendments to the REC will be prepared and submitted under the King's CTU's supervision, whilst all Substantial amendments to the MHRA, and the DSUR will be prepared and submitted by the KHP-CTO.

6.4.1 IMP supply

- O-NTX - The co-ordination of the IMP supply will be undertaken on behalf of the Co-sponsors by ModePharma. O-NTX (50mg) will be sourced and matching placebo manufactured, packaged and labelled in accordance with Good Manufacturing Practice (GMP) to ensure robust blinding. Each treatment pack will be allocated a unique ID number, which will link directly to the online randomization system to ensure that the IMP supply is managed appropriately.
- XR-NTX - Implantable XR-NTX iGen/Atral-Cipan device (Naltrexone 765mg implant) and matching placebo will be supplied by the manufacturer. Each treatment pack will be allocated a unique ID number, which will link directly to the online randomization system to ensure that the IMP supply is managed appropriately.

6.4.2 Trial medication packaging and labeling

Packaging and labelling will be completed in accordance with GMP and Good Clinical Practice (GCP), arranged by ModePharma, Bromley.

- O-NTX - Active and placebo oral medications will be packaged identically in blister strips .
- XR- NTX Active and placebo implant devices will also be packaged identically.

6.4.3 Dispensing and distribution

O-NTX and matching placebo will be distributed to the centre pharmacies via ModePharma, active and placebo implants will be distributed to the sites directly from iGEN. The randomisation system will be linked to the IMP supply, with the unique treatment kit number to be prescribed for the oral medication and also the single unique implant pack allocated by the system at randomisation. Prescriptions and a copy of the randomisation email confirmation will be submitted to the dispensing pharmacy. An automatic alert will be generated and sent to the Trial Manager if supplies are running low at a particular site. Receipt of medication will be recorded in the study pharmacy file. A study medication dispensing and return log will be maintained by the centre pharmacies.

- XR-NTX: Implantable study medication will be dispensed on the day of administration.
- O-NTX: Oral medication will be dispensed by each centre's pharmacy to the outpatient's clinic as one pack for the first 4 weeks, where it will be stored until administered, as per routine clinical practice, and additional records will be maintained. On weeks 5 to12 O-NTX will be issued once a week and given to the patient for self-administration. Oral medication packs will be returned to the main dispensing pharmacy for reconciliation. In weeks 1 – 4 small doses may be given as take away medication if clinic attendance is impossible (e.g. due to court appearances, urgent hospital appointments etc).

Administration records from outpatients will be retained and monitored by the Trial Manager and reviewed at KHP-CTO monitoring visits, to ensure that accurate CRF data on doses administered are recorded. After the week 12 visit, all study medication will stop and patients will not be offered further NTX treatment as part of the trial. Individual clinicians may continue prescribing to patients if this is clinically appropriate.

6.5 Dosing Regimen

6.5.1 Interventions

Oral medication will be administered under direct supervision in the outpatients clinics on Mondays (100mg), Wednesdays (100mg) and Fridays (150mg, a higher dose to last till Monday) for the first 4 weeks. Oral medication during weeks 1-4 will be directly observed. Small doses may be given as take away medication if clinic attendance is impossible (e.g. due to court appearances, urgent hospital appointments etc). Contingent on good adherence during the first month, patients will be able to self-administer oral medication (weeks 5-12 dispensed on a week by week basis and contingent on attendance at the clinic three times a week to complete research measures and return packaging and report dosing. If there are any adherence problems, the patient will be supervised for 2 weeks and will return to self-administration if adherence picks up.

The single iGen/Atral-Cipan device will be administered on a day-patient basis by a centre doctor (a local GP, or hospital physician) appropriately experienced in general practice minor surgical procedures. We will secure a clinical consultant with extensive experience in these procedures to guide our training programme. The implant procedure will take approximately 30 minutes, in an appropriate clinical facility attached to each centre with one of the two trial nurses assisting. A single-use minor surgical pack will be used for each procedure.

Each participant will be scheduled to receive the following study interventions:

- 1 iGen/Atral-Cipan (XR-NTX) implant (765mg) or matching placebo at Day 0 of Study Week 1.
- 3 x O-NTX tablets (2 x 50mg, Monday and Wednesday; 3 x 50mg, Friday) or matching placebo at Day 0 of Study Week 1 (for 12 weeks), directly observed for first 4 weeks and then patient reporting self-consumption for next 8 weeks when attending clinic to complete research measures. (NB: The higher dose given on Fridays is to cover the weekend period).

The oral placebo tablet has the same excipients as the active medication. The tablet core contains: lactose Anhydrous, lactose monohydrate, microcrystalline cellulose, and magnesium stearate. Each tablet is film-coated with: Opadry II Yellow and purified water pheur. .

6.5.2 Follow up

There are three follow-up assessments: at 16, 24 and 36 weeks Each of these follow-ups is trial nurse-administered and held in a private clinical room at the recruitment centre. A long recognised problem in conducting outcome studies with drug users is the difficulty in following up participants for research interviews, particularly where patients have dropped out of treatment and are no longer in contact with the treatment service. To overcome this potential problem, information will be collected from patients at the beginning of the study that will assist researchers in tracking patients. This will include postal addresses and telephone numbers of patients, contact details of at least one locator individual (e.g. a family member, friend or recovery mentor), and permission to contact authorities such as general practitioners. Patients will be given assurances that all attempts to contact them will be confidential, and the purpose of the researchers seeking contact will not be disclosed to others. Patients will be reimbursed for their travel costs to attend clinic visits, and will also receive a high street store voucher worth £20 in return for the time taken to attend each of the three 60 minutes post-treatment follow-ups

6.5.3 Post trial treatment

After the 12 weeks of trial treatment, participants will be free to continue to receive keyworker facilitated case management support as normal. After each eligible participant has completed their follow-up at 36 weeks (i.e. those who are abstinent from heroin and have no opioid tolerance), they will be referred for further clinical assessment and as appropriate, will be offered six months of O-NTX as routine practice. Each participant who completes the trial will be recommend to attend self-help group meetings and contact their local NHS addictions service for support and further treatment as needed.

6.6 IMP Risks

The Investigators Brochure (IB) will be the primary reference document for all information pertaining to IMP risk for the Naltrexone implant, supplemented by a recent systematic review of research studies[xxii]. From the IB, the risks and contra-indications include:

A. Transient-General (mild-moderate adverse events). The most common AEs are: abdominal discomfort, nausea and drowsiness. Headache, nausea, vomiting and muscle pain, diarrhoea, irritability and anxiety have also been reported among research trial participants.
B. Site-related-Specific (mild-severe adverse events). Pain, induration (redness and swelling) and, rarely, local allergic tissue reactions, wound opening and infection may be experienced when administering XR-NTX.

From Larney et al22.:

A. Implantation site-related AEs (from three trials) are more likely among those receiving active rather than placebo XR-NTX (relative risk 4.68; 95% CI 1.63 to 13.44; moderate quality evidence).
B. No difference in rates of opioid overdose between XR-NTX and O-NTX (moderate quality evidence).

However, there may be bias in the scientific literature on NTX AE risk due to incomplete data (e.g. AEs not completely reported among participants who drop out of trials).

For Oral Naltrexone, as this is a licensed product in the UK, the Summary of Product Characteristics (SmPC) will be the reference document and the risks and contra-indications include:

Contraindications

A. Hypersensitivity to naltrexone hydrochloride or to any of the excipients
B. Acute hepatitis
C. Severe hepatic impairment
D. Severe renal impairment
E. Opioid addicted patients with a current abuse of opioids, since an acute withdrawal syndrome may ensue.
F. Positive screening result for opioids or after failure of the naloxone provocation test.

Undesirable effects include:

A. Very common effects - nervousness, anxiety, sleep disorders, insomnia, headache, abdominal pain, abdominal cramps, nausea, emesis, joint and muscle pain, feebleness
B. Common effects - loss of appetite, irritability, mental disorder disorientation, nightmares, restlessness, abnormal dreams, increased tear secretion (lacrimation), tachycardia, heart palpitation, anomalies in the ECG, pain in the chest, dyspnoea, diarrhoea, constipation, dermatitis, pruritus, rash, urinary retention, delayed ejaculation, decreased potency, libido disorders, thirst, increased energy, weight loss, weight gain, fever, pain, sensation of cold in extremities, hot flashes, fatigue, dizziness, stupor,
C. Uncommon effects - oral herpes, athlete's foot, lymphadenopathy tremor, vision disorders, irritation and swelling of the eye, photophobia, eye pain or tiredness, colour asthenopia, ear disorders, ear pain, tinnitus, vertigo, oedema, hypertension, blood pressure changes, flushing, nasal congestion, nasal disorders, rinorrhoea, sneezing, oropharyngeal disorders, increased sputum, sinus disorders, dysphonia, coughing, yawning, flatulence, haemorrhoids, ulcus, mouth dryness, hepatic disorders, increased bilirubin levels, hepatitis (During treatment, increase of transaminases is possible. After discontinuing the intake of Adepend, transaminases decrease to the original levels within some weeks.), seborrhea, acne, alopecia, groin pain, pollakisuria, dysuria, hallucination, confusion, despondency, depression, paranoia
D. Rare effects - suicidal ideation, attempted suicide, speech disorders, syncope, idiopathic thrombopenia,
E. Very rare effects – rhabdomyolysis

6.7 Drug Accountability

Used treatment packs will be obtained from the outpatient clinics at week 16. Pharmacy departments in each centre will maintain a study medication dispensing and returns log, including date dispensed, batch number, expiry date, number of implants and tablets dispensed, study medication return date and amount of study medication returned. In addition, the study specific prescriptions will be maintained in the pharmacy file for audit purposes. Study medications returned to pharmacy will be destroyed by the pharmacy after primary analysis is complete, and once approval has been obtained from the KHP-CTO CRA and PI. The researcher will count the medication returns and enter the information on the eCRF. The KHP-CTO CRA will cross-check this information with the pharmacy records during site visits and re-count tablets if there is any discrepancy. The pharmacist or researcher will then amend the incorrect record. As the implanted Naltrexone dissolves *in vivo*, there will be no returned products, however empty packaging should be returned to pharmacy.

6.8 Participant Compliance

Participant compliance will be measured through supervised oral naltrexone dispensing records and through attendance records. If a patient misses a dose, they should take the next one as prescribed. If they lose medication, they should contact the study team immediately for a replacement.

6.9 Concomitant Medication

Each participant's use of concomitant medications will be reviewed once a week at the study visits. The Investigator will record all medication used by the participant. This record will include the name of the medication, the dose, route of administration, regimen, dates when drug was started and stopped, and the indication for drug use.

Permitted agents included anticonvulsants if dosing was stable and short-acting PRN insomnia medications, e.g., zopiclone (Imovane, Ivadal). Prohibited medications include: naltrexone, buprenorphine, levomethadyl acetate/LAAM, methadone and other prescription opioids.

In an emergency situation in patients receiving naltrexone, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required as part of anesthesia or analgesia, such patients should be continuously monitored, in an anesthesia care setting, by persons not involved in the conduct of the surgical or diagnostic procedure.

For management of concomitant therapies, please refer to the NEAT trial Investigators Brochure (section 6.3 to 6.7).

6.10 Concomitant Therapy

6.10.1 Case management and reinforcement protocol

- 1 x weekly standard clinical case management sessions (for 12 weeks) using mapping-based task- and goal-setting tools and a general relapse prevention skills training and craving coping approach.

Participants will receive a package of best supportive care with 12 weekly sessions of practical, manual-guided, personal goal-setting and relapse-prevention oriented counselling with a clinic keyworker. Each patient will also have appointments with their prescribing physician (the clinic centre PI) on a monthly basis, or more frequently, if required.

In NHS outpatient addiction clinics each patient is assigned a keyworker to provide case management and to support the patient through their intervention pathway across regular clinic appointments. The keyworker gives practical advice and applies psychological techniques, building motivation to reduce drug-related harms, prevent relapse, and also organising required access to community services. A practical goal-setting and relapse-prevention protocol will be delivered based on node-link mapping techniques to provide an effective method of helping the patient identify personal goals and monitor tasks[xxiii, xxiv]. Mapping is a counseling tool that has been adapted in the UK and reflects four key elements of the counseling process:

- *Communication*: using maps can provide a clear visual representation to help the communication skills of the patient;
- *Focus*: maps provide a way to cluster and summarise information to guide and focus a discussion and maintain attention. Evidence suggests that maps help counsellors and patients maintain their focus;
- *Producing ideas*: node–link maps can provide a strategy for idea generation, and may also facilitate causal thinking by making patients examine what influences their behaviour, or what may happen next. This process may be most useful when therapists and patients are struggling to remember details, or are in need of a fresh approach; and
- *Memory*: Memory for session information is related to the effectiveness of counselling. Node–link maps have been shown to enhance the recall of information in both educational and clinical settings.

6.10.2 Reinforcement protocol (incentivised clinical attendance)

- 3 x weekly behavioural reinforcements to attend the clinic for O-NTX doses and to complete assessments in each of 12 weeks, with an ascending voucher-based schedule (contingent on attendance and ingestion of medication).

Given the well-recognized problem of O-NTX adherence, a clinic attendance reinforcement protocol will maximize adherence to trial medication. This is as recommended by NICE (2007). The theoretical model underpinning this approach is contingency management (CM), a form of behaviour therapy in which a tangible reinforcement, contingent on a sought behaviour, is elicited from a participant. This, in turn, increases the probability of a subsequent desired response[xxv]. Research in the target populations indicates that one of the most effective protocols links each successive behaviour elicited with an increase in the level of reinforcement, thereby increasing motivation[xxvi].

Effective CM interventions have the following features: first, the clinician arranges the environment so that target behaviours (e.g. drug abstinence, clinic attendance, medication compliance) are readily detected. Second, incentives are provided when the target behaviour is demonstrated, and third, incentives are withheld when the target behaviour does not occur. In addition to three randomized controlled trials of O-NTX compliance using CM techniques for opioid dependence, the meta-analysis by NICE indicates a medium to large effect[xxvii].

In the NEAT trial, an incentive will be offered to each participant for attending the clinic. This will be a trial nurse-administered, voucher-based reinforcement protocol, contingent on attendance to screening visits and then thrice-weekly during weeks 1-12) to provide urine samples and complete research measures. Participants will receive non-cash high street store vouchers that can be exchanged for recovery appropriate goods and services. Starting at a low level (£5 in value), the reinforcement value then increases at a set rate for each attendance. If a participant attends for each of their 37 clinic appointments, they can receive vouchers worth a total of £400.

7. Selection and Withdrawal of Participants

7.1 Inclusion Criteria

Inclusion criteria for the study are intended to be as close to clinical practice as possible. Each participant in the trial must meet all of the following criteria:

1. Is 18 years of age or older.

2. Can demonstrate a verbal understanding of the study patient information material, is able to provide written consent, and can understand and confirm willingness to comply with the protocol.

3. Has a diagnosis of opioid use disorder based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM5: past 12 months),) conducted at baseline.

4. Is completing or has recently completed an inpatient or outpatient treatment for opioid detoxification, or has been completely and continuously abstinent from all opioids for at least seven days.

5. Has no tolerance to opioids, as verified by a negative urine toxicology screening test prior to randomisation (using an instant result immunoassay device).

6. Passes a naloxone challenge test (to confirm zero opioid tolerance by demonstrating no clinical sign or subjective report of opioid withdrawal before randomisation and prior to implant procedure) NB: Individuals failing screening will be allowed to enter screening as clinically indicated.

7. Is voluntarily seeking opioid antagonist treatment for opioid use disorder.

8. Lives in stable/secure accommodation in the community.

9. Has a personal (mobile/cellular) phone, and is able to nominate at least one locator individual (e.g. a family member, friend or recovery mentor) with a verifiable address and a telephone number to assist with the arrangement of follow-up appointments as required.

10. If female, is not pregnant or breast feeding and agrees to use a birth control method (either oral hormonal contraceptives, barrier [condom or diaphragm], or Nexplanon implant) for the duration of the study.

7.2 Exclusion Criteria

Otherwise eligible individuals who meet any of the following criteria will be excluded from the study:

1. Clinically significant medical condition or observed abnormalities on physical examination or laboratory investigation, including but not limited to:

    - Uncontrolled hypertension;
    - Significant heart disease (including angina and myocardial infarction in past 12 months);
    - Any ECG/cardiovascular abnormality which, in the investigator's judgment, is clinically significant.

2. Severe alcohol dependence and/or alcohol withdrawal (by clinical assessment).

3. Opioid withdrawal syndrome, current.

4. Positive test for presence of opioids in urine (i.e. indicating current opioid use) prior to randomisation (using an instant result immunoassay device).

5. Clinical diagnosis of opioid dependence syndrome (F11.2) with current physical dependence such that an antagonist medication (e.g. naloxone, naltrexone) could precipitate a withdrawal syndrome

6. Positive naloxone challenge test at randomization (confirming opioid use) or absence of a recorded result from a naloxone provocation test.

7. Acute hepatitis taken as clinical jaundice on examination and/or blood bilirubin level >normal range for local reference criteria or aspartate aminotransferase or alanine aminotransferase (>3x the upper limit of the normal range).

8. Hepatic insufficiency (taken as >3 times the upper limit of the normal range of aspartate aminotransferase or alanine aminotransferase)

9. Severe renal impairment evaluated by clinical decision

10. Known Icenko-Cushing syndrome or to require investigation if suspected Cushingoid features/symptoms

11. Systemic mycoses

12. Clinical history of glaucoma

13. Clinical history of osteoporosis

14. pregnancy, or positive or unclear test result from pregnancy test, or intention to try to become pregnant during the study period, or is sexually active without using a birth control method (either oral hormonal contraceptives, barrier [condom or diaphragm], or Nexplanon implant) for the duration of the trial.

15. Currently breast-feeding
16. History of hypersensitivity to opioid receptor blockers (naloxone and naltrexone formulations) and other components of the formulation.
17. History of hypersensitivity to triamcinolone or related compounds
18. Currently taking oral or depot naltrexone therapy or enrolment in any form of naltrexone therapy within 90 days prior to study screening, apart from treatment given by trial team between screening and the start of treatment.
19. Current criminal justice involvement with legal proceedings (not including current probation supervision) and, in the opinion of the clinical worker, is expected to fail to complete the study protocol due to re-incarceration or relocation from the centre's catchment area.
20. Current (past 30 day) suicidal planning, or recent (past six months) suicide attempt.
21. Active, uncontrolled severe mental illness (e.g. psychosis, bipolar I disorder, schizoaffective disorder) and/or a history or evidence of organic brain disease or dementia that would compromise the participant's ability to comply with the study protocol.
22. Current participation in any interventional trial, or completed participation in any interventional trial (which in the view of the chief investigator might interfere with the NEAT trial) within the last 3 months

7.3 Selection of Participants

The trial will be implemented in two well-established specialist NHS outpatient addiction clinics in London and Birmingham. (recruitment centres), each with the local University and with existing collegiate links for research trials.

In each clinic, we will promote the availability of the trial to four groups of potentially eligible patients as follows:

A. those currently receiving outpatient treatment, either opioid agonist maintenance therapy, or detoxification therapy;
B. those currently receiving outpatient or inpatient (London and Birmingham) opioid detoxification;
C. formerly dependent heroin users who are now drug-free and receiving abstinence supportive counselling; and
D. new patient referrals with opioid dependence who wish to become drug-free and receive abstinence therapies. According to the clinical presentation, this group will receive agonist pharmacotherapy as a short-term stabilisation phase before entry into detoxification, or will proceed directly into detoxification.

7.3.1 Advertising the study to the prison population

Given the link between opioids and acquisitive crime, there is a high prevalence of inmates in the English prison system with opioid dependence histories. The London and Birmingham. treatment clinics operate satellite prison healthcare services for addiction treatment in local prisons. In London, Lorraine Hewitt House operates a clinic in HMP Brixton (male category B remand); and in Birmingham the Slade Road Community

Drug Team operates a clinic in HMP Winson Green (male category B). Information about the trial will be provided to prison health care teams. Potentially interested individuals will be invited to contact the NEAT research team on their release to complete screening and consent procedures at each community treatment centre.

7.3.2 *Patient Identification Centres*

There is potential for patients to be referred to the London and Birmingham treatment centres from both NHS and non-NHS institutions. These institutions will be listed as Patient Identification Centres. These institutions can then identify participants, can provide information about the study, can advertise the opportunity to participate in the study, (eg via posters in waiting rooms) or can put potential participants' in touch with the NEAT research team.

7.4 Randomisation Procedure / Code Break

Randomisation will be requested by study sites online using a bespoke web based randomisation system hosted at the King's CTU.

Only study site staff authorised by the trial manager will be given login details to the randomisation system. Authorised staff will be allocated a username and password for the randomization system. Once a patient is consented, all baseline data collected and eligibility confirmed, the staff member will log into the randomization system (www.ctu.co.uk and click "randomisation – advanced" and select NEAT study) and enter the patient's details. The "help" section of the system has video demonstrations to aid new staff in using the system. Once randomized, the system automatically generates confirmation emails to key staff, with or without treatment allocation information, depending on their role in the study.

Emergency 24 hour code break will be via the eSMS emergency service (Medical Toxicology Information Service). Patients will be given a card to carry throughout the study, which gives details of the emergency code break telephone number to be called in the event of a clinical emergency necessitating code break. The eSMS 24 hour service number is 0203 282 0458

7.5 Withdrawal of Participants

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations, administrative reasons or other reasons. Upon withdrawal from the study the patient will be asked to complete the Treatment Outcomes Profile (TOP) and the withdrawal form.

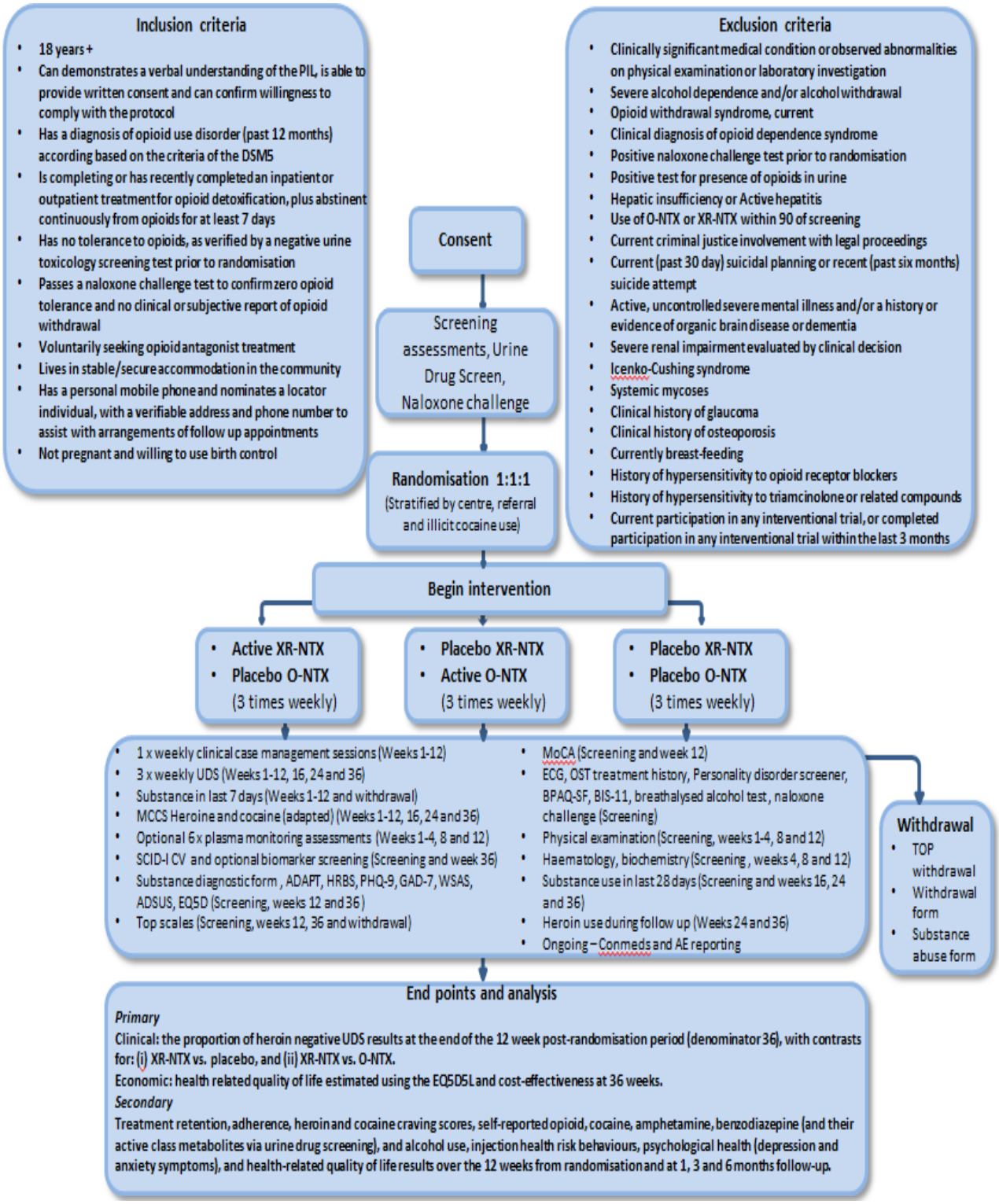
It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a patient withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

7.6 Expected Duration of Trial

Expected clinical participation for each participant is from consent until the final follow-up at 36 weeks (38 weeks in total). The study will begin when the first participant gives consent and will end when the last participant has finished the follow up assessment at 36 weeks.

8. Trial Procedures

8.1 Trial Flowchart



8.2 Informed consent

Potential participants will be approached by a member of the clinical team. Each screening procedure will be overseen by the centre PI, or a medical officer reporting to the PI. Individuals failing screening will be allowed to enter screening once more (only) after 1 month.

A study doctor or trial nurse will implement the enrolment procedure and obtain informed consent. In cases when the taking of consent has been appropriately delegated to a non-physician, patients should be offered the opportunity to speak with the study doctor and the study doctor must document that they have confirmed the patient's eligibility in the medical notes, before the patient is randomised. The study information sheet will be read to the potential participant and discussed to ensure that he/she fully understands the purpose and key conditions of the trial, what is required and the risks and benefits arising from taking part. Each interested participant will receive an informed consent document with participant information and will be asked to read the information and ask questions.

If the patient wishes to participate, he/she will be required to sign the informed consent document prior to the conduct of any study-specific clinical procedures. This document will be witnessed and singed by the clinical worker.

In addition (and not a requirement of participation in the trial), participants will be asked if they are also willing to participate in collection of venous blood samples at intervals over the course of their treatment to enable study of blood levels of naltrexone and its metabolites. For participants wishing to participate, a written record of their consent will additionally be collected (as above). This will be considered separately.

8.3 Vital signs

In addition to the recording of demographic, social circumstances, referral information, substance problems treatment history and past 12-month DSM-V diagnostic criteria for opioid, cocaine, amphetamine, cannabis, sedative and alcohol dependence, and an instant result immunoassay test at screening, each participant will complete a physical exam administered by a clinic doctor or nurse, recording: height, weight, systolic/diastolic blood pressure and pulse rate (screening, 1, 2, 3, 4, 8, 12) and 12-lead ECG, measured after 5 minutes in a seated position (screening).

8.4 Plasma monitoring

6-β-naltrexol is the primary metabolite of NTX. We plan to recruit, from the NEAT study sample, a sufficient number of participants to enable examination of plasma levels of 6-β-naltrexol as well as of naltrexone itself, and to study the relationship to clinical benefit. Whilst outside the scope of the NIHR funded work, we present a summary of these analyses.

6-β-naltrexol is the primary metabolite of NTX. Maintaining stable levels of this metabolite is the key aim of both O-NTX and XR-NTX and a key indicator of therapeutic response and benefit. Stable levels of 6-β-naltrexol correlate with opioid craving levels and falling levels of 6-β-naltrexol may correlate with attenuating patient engagement in the relapse-prevention therapeutic programme and drop-out. Subject to voluntary participant consent, assessment of 6-β-naltrexol at regular intervals in the first month of treatment is important to document the intended action of active NTX and at later weeks to show: (1) the stability of the active implant; and (2) patient compliance with active O-NTX. Accordingly, 6-β-naltrexol will be assessed on six occasions (weeks 1, 2, 3, 4, 8 and 12). At each clinical centre, EDTA blood (3-5 mL) will be collected via venepuncture. Samples will be centrifuged one portion to harvest plasma (1 mL) and the remainder is kept as whole blood (and store at -20 C in batches prior to laboratory processing at the co-ordinating centre [Toxicology Unit, King's College Hospital; Professor RJ Flanagan]).

8.5 Biological testing of opioid, cocaine, amphetamine and benzodiazepine use

At screening and thrice weekly until week 12 (plus all follow up weeks), participants will be asked to provide a clinic procedure supervised urine test for opioid, cocaine, amphetamine and benzodiazepine use. The study will use an instant result immunoassay device.

This is a tamper-proof device with a 48-hour detection window for opioids, cocaine, amphetamine and benzodiazepine metabolites with a temperature sensor required to register 33° - 38° C. This provides an instant qualitative test for recent drug use and will be used for the treatment responder/non-responder categorisation and outcome measure.

8.6 Naloxone challenge

Participants will be given naloxone prior to randomising the patient on week 1, with monitoring over 30 mins to check for no sign of opioid withdrawal. Individuals failing screening will be allowed to enter screening once more (only) after one month.

8.7 Breathalysed alcohol level

At screening and prior to the implant procedure, all participants will be breathalysed to exclude alcohol intoxication. Participants with a breathalysed alcohol level >0.35mg/l (35 Milligrams of alcohol per litre of breath) cannot proceed with screening or the implant procedure. NB: Individuals with breathalysed alcohol level >0.35 will be allowed to re-enter screening as clinically indicated

8.8 Self-reported substance use

Each participant will be asked to report their use of illicit opioids, cocaine, amphetamine alcohol and benzodiazepine.

At Screening and during weeks 1 to 12, data will be collected weekly for the 7 days prior to the visit, using the 7 day drug and alcohol use self-report form.

In the follow up stage, data will be collected at weeks 16, 24 and 36 for the 28 days prior to the visit, using the 28 day drug and alcohol use self-report form.

8.9 Molecular biomarker screening (genotyping)

Subject to voluntary participant consent, participants will be invited to allow the research team to undertake a genotyping targeting candidate pharmacodynamic biomarkers of addiction treatment response addiction risk vulnerability (including but not limited to OPRM1, OPRMD1; OPRK1; ORL1; CNR1 and DRD2 [stimulant risk], POMC [multiple substance risk]) and moderators of corticotropic stress and memory function (e.g. FKBP5, CRHR1 and NR3C1/2). DNA will be extracted from a single oral fluid sample collection and stored at the Social, Genetic and Developmental Psychiatric (SGDP) Centre at the Institute of Psychiatry, Psychology & Neuroscience on weeks -2 and 36. The sample collection procedure uses a pre-packed set of 10 cotton 'Q-Tip' buds. The participant opens the pack and rolls each Q-tip slowly and individually around each cheek area (5 on the left side and 5 on the right) and places each one in a 15cm plastic collection tube which holds all 10 Q-tips. The collection tube contains 10ml of neutral buffer solution. The cap is sealed by the participant and a bar code label is placed on the tube and sealed in a transit ziploc plastic bag for transport to the SGDP laboratory. Taking part in this aspect of the trial is entirely voluntary and an individual can enroll in the NEAT trial and decline to participate in the biomarker study. The biomarker study seeks to build on a research programme of studies in this area conducted at the trial coordinating centre (Institute of Psychiatry, Psychology & Neuroscience by Lead Investigator John Marsden [e.g. REC 10/H0808/73]) and with other university collaborators.

8.10 Structured clinical interviews and instruments

Participants will complete the following structured clinical assessments and instruments during the course of the study:

- DSM5 Axis I disorders: *major depressive episode* (current [2 weeks]; past; recurrent); *suicidality* (current [past month]; *panic disorder* (current [past month]; lifetime); *post-traumatic stress disorder* (current [past month]); *generalized anxiety disorder* (current past 6 months); *anti-social personality disorder* (lifetime), via SCID V[28]. Screening and week 36.
- Drug and alcohol use 7 day form- Weeks 1 to 12.
- Minnesota Heroin [adapted] Craving Scale (MCCS for Heroin) Once at screening, then weekly until week 12, once at each follow up visit on weeks 16, 24 and 36 thereafter.
- Minnesota Cocaine [adapted] Craving Scale (MCCS)[29] Once at screening, then weekly until week 12, once at each follow up visit on weeks 16, 24 and 36 thereafter.
- Borderline Personality Disorder Screener (BPD)[30]* - Screening.
- Short-form Buss-Perry Aggression Questionnaire (BPAQ-SF)[31]* - Screening.
- Barratt Impulsiveness Scale (BIS-11)[32]* - Screening.
- Addiction Dimensions for Assessment and Personalised Treatment (ADAPT) - Screening, weeks 12 and 36.
- Montreal Cognitive Assessment (MoCA)[33]. - Screening and week 12.
- HIV Risk-taking Behaviour Scale (HRBS)[34] - Screening, weeks 12 and 36.
- Scales (TOP)[35] - Screening, weeks 12, 36 and at withdrawal.
- Patient Health Questionnaire (PHQ-9)[36] - Screening, weeks 12 and 36.
- Generalized Anxiety Disorder Scale (GAD-7)[37] - Screening, weeks 12 and 36.
- Work & social adjustment scale (WSAS) - Screening, weeks 12 and 36
- EQ5D [38] - Screening, 12 and 36.
- Alcohol and Drug adapted Adult Service Use Schedule (AD-SUS). - Screening, 12 and 36.
- Drug and alcohol use 28 day form – Screening and weeks 16, 24, and 36 (and at withdrawal if withdrawal is after week 12)
- Heroin use form – weeks 24 and 36 (and at withdrawal if withdrawal is after week 12)
- AE & conmed forms - Ongoing.

The instruments above marked by an asterisk are for participant self-completion (assisted by a NEAT worker as required). These measures will be gathered and screened in the analysis as moderators of treatment response. The clinical team will use the information collected as part of the case formulation, treatment planning and tailoring process.

8.11 Laboratory Tests

Blood samples for hematology and biochemistry analysis will be collected at weeks -2 (unless there is historical blood test less than 2 months old) and then on weeks 4, 8 and 12 thereafter for the following assessments: full-blood count (hematocrit, hemoglobin, red/white blood cell count and platelets); and biochemistry (sodium, potassium, glucose, creatinine, protein, bilirubin, alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, alkaline phosphatase, and creatine phosphokinase).

9. Assessment of Effectiveness

A comprehensive analytic strategy will be developed and agreed with the trial's governance committees. Estimates and confidence intervals will be presented for differences over treatment groups. Sensitivity analyses will be used to assess the robustness of conclusions to missing outcome data and to departures from randomized treatment. Loss to follow-up, departures from randomized treatment and the prevalence of serious adverse events will be reported at 1, 3 and 6 months post randomization.

9.1 Primary Effectiveness Parameters

The analyses of effectiveness will be pragmatic, based on the intention-to-treat sample, and will utilise all available follow-up data from all randomised patients. The proportion of heroin negative urines at the end of the study period (denominator 36) will be analysed with a regression model adjusted for stratification factors (centre, referral and recent cocaine use) with contrasts for: (i) XR-NTX vs. placebo, and (ii) XR-NTX vs. O-NTX at 12 weeks post-randomisation. The most conservative approach (and used by previous trials) is to record DNA or refused clinic visits and urine samples as positive. A multiple imputation strategy will be approved by the Trial Steering Committee.

9.2 Secondary Effectiveness Parameters

Between treatment retention will be evaluated with Kaplan-Meier curves and log-rank analyses. Adherence will be compared across treatment arms using Chi-square analysis. Other secondary outcomes with repeated measures (such as weekly craving scores; self-reported heroin, cocaine, benzodiazepine, alcohol use) over the 12 weeks will be analysed using longitudinal linear models with adjustment for the stratification factors listed above, treatment arm and baseline values. Chi-squared (Fisher's exact) tests will be used for categorical outcomes (serious adverse events and mortality). Patterns of heroin relapse between treatment arms will be analysed using a latent transitory model

10. Assessment of Safety

10.1 Specification, Timing and Recording of Safety Parameters.

In each clinical recruitment site, patients will be asked to give blood samples for liver function (hepatotoxicity) testing during screening and monthly over the course of active treatment (weeks 4, 8 and 12). Samples will be analysed at the local hospital pathology service, with the following clinical biochemistry assays conducted: albumin, bilirubin, liver transaminases (AST/ALT (SGOT/SGPT) and transaminases.

Safety reporting will follow the requirements described in The Medicines for Human Use (Clinical Trials) Regulation 2004: SI 2004/1031 and the EU Directive 2001/20/EC. Each participant will be given a study identification (ID) card which describes the trial and provides the following information: some cough and cold medicines containing opiates may not work as well as they should and alternatives will be recommended; emergency pain relief following an accident may not be achieved using opiates; taking an extremely large dose of heroin to overcome NTX blockade could result in serious overdose; and there will be sensitivity to small doses of opiates after discontinuing NTX. The patient ID card will list telephone contact information to enable emergency unblinding. A 24-hour emergency code break will be available through ESMS, London.

All cause withdrawal from randomised treatment will be reported at months 1 and 3 post randomisation. The prevalence of specific adverse events and reactions will be reported descriptively at 1, 3 and 6 months post randomisation. Treatment stops at 3 months so adverse events and reactions recorded post this data will be specific to this follow up period (such as overdose, heroin lapse and relapse). The prevalence of patients experiencing one or more serious adverse events will be compared at 1, 3 and 6 months post randomisation across the three trial arms (as randomised) using Chi Square tests. Mortality prevalence will be considered independently to any other serious adverse events.

It is possible that the NTX implant procedure will lead to local site infection or other complications. Prophylactic anti-biotic medication can be used post-surgery and participants will be monitored and checked by the trial nurse on each clinic visit and by each centre PI (physician) each month. Site inflammation will be man managed on a case-by-case basis, and likely to involve steroidal anti-inflammatory treatment. All serious and non-serious adverse events identified after randomisation until 16 weeks post-randomisation will be reported, irrespective of causality.

10.2 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a participant to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

The summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)

The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

Important Medical Events (IME) & Pregnancy

Events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Although not a serious adverse event, any unplanned pregnancy should be reported via the SAE reporting system as stated below.

Reporting Responsibilities

King's College London & South London and Maudsley NHS Foundation Trust have delegated the delivery of the Co-sponsors' responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs will be reported immediately (and certainly no later than 24hrs) by the Investigator to the KHP-CTO and CI for review in accordance with the current Pharmacovigilance Policy.

The adverse event form (AEF) will be reviewed at each trial assessment clinic visit (thrice weekly during weeks 1-12), at the 16, 24 and 36 week follow-ups, and following any occurrences in between study visits and follow-ups. All clinical investigators in the study will be provided with full details of possible adverse medical events that may result from the trial medication and/or procedure, as well as other possible occurrences that may not be caused by or related to that product or procedure.

Any adverse events occurring during the trial will be recorded in the participant's source data worksheet and filed in their medical records at the end of the trial. They will also be transcribed on to

the electronic Case Record Form (eCRF). A decision and reporting flowchart will be developed for the management of adverse events, and all research workers and investigators will receive training on safety issues and notification procedures.

Clinicians will report, and the centre Principal Investigator (PI) will assess, each adverse event for seriousness, causality (relationship to trial IMP: definitely related, likely, possibly, unlikely or not related), expectedness, and intensity (mild, moderate and severe). Copies of any SUSAR (suspected unexpected serious adverse reaction) will be sent to the Chair of the DMC. The centre PI (or clinician delegated to undertake this task) will sign the SAE report form on paper. The Trial Manager will manage SAEs outside the eCRF in order to comply with KHP-CTO procedures. The KHP-CTO CRA will issue queries on the SAE during monitoring visits to collect follow-up information until resolution of the event, and basic event information will be entered on the eCRF.

The CI (or a doctor nominated by the CI) will review every event within one working day of the SAE form being received and determine whether the event was expected or unexpected. The CI may upgrade the intensity or causality of an event without the centre PI's agreement, but only the centre PI will be permitted to downgrade the event based on further follow-up information. If the clinical co-ordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, will be instructed to write through the Trial Office to the Chair of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

On a scheduled basis, the DMC will perform an integrated safety analysis of all adverse event information reported and ensure discussions are held and actions undertaken to secure the safety of all participants. If necessary, discussions may result in the trial's discontinuation. At the end of the fieldwork phase of the study each centre PI will write formally to the clinician assuming responsibility for the participants' ongoing clinical management, informing of them of any unresolved adverse events.

The KHP-CTO will report SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- KHP-CTO (on behalf of the co-sponsors), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

10.3 Staff training

In accordance with high standards of research governance we will ensure that all researchers receive training in Good Clinical Practice (GCP). All staff employed on the grant and all investigators will be trained in GCP, use of the assessment tools, and trial standard operating procedures. Up-to-date CVs of all staff working on the trial will be kept in the Study Office, together with a log of all relevant training received by staff.

10.4 Treatment Stopping Rules

The trial may be prematurely discontinued by the Co-sponsors, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring Committee / Trial Steering Committee regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from a Trial Steering Committee (if applicable), who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

11. Economic evaluation

Given that implanted XR-NTX is currently an unlicensed medication in Europe, and is more expensive than O-NTX, the relative cost-effectiveness of XR-NTX and O-NTX treatments will be assessed by including opportunity costs for stakeholders and comparing ratios of incremental opportunity costs (for all stakeholders) and incremental outcome (health related quality of life). Costs of the study interventions, external health services, and expenditure by the social and criminal justice sectors will be combined with the primary clinical outcome measure and quality adjusted life years to produce incremental ratios that will determine relative cost and cost-effectiveness.

Economic outcome assessments will be carried out after the 12-week treatment period and at the 36 week follow-up. The *a priori* primary economic outcome measure will be quality adjusted life years using the EQ-5D. The economic evaluation will take a broad policy perspective, including costs borne by hospital and community health and social services and the criminal justice sector, plus the costs of criminal activity. Detailed information on the resources associated with the treatments, including study medications, equipment, dispensing services, urine tests, nurse time, and contacts with key workers, medical, nurse and psychology staff, will be collected from clinical records. Resources external to the clinics, including staffed/supported accommodation, hospital contacts, community health and social services, criminal justice sector resources and crimes committed will be collected in interview with study participants at baseline, after the 12 week treatment period and at the week 36 follow up.

11.1 Costs

Intervention costs will be calculated using a standard micro-costing (bottom-up) approach to incorporate the cost of all elements of the intervention (medications, equipment, dispensing services, urine tests and nurse time), plus appropriate clinic and managerial overheads. If relevant, adjustments will be made in sensitivity analysis to better reflect the long-term costs of the interventions in routine clinical practice. For example, this may involve assessment of potential changes to the supply and thus the cost of XR-NTX if demand in routine clinical practice is anticipated to increase as a result of the trial's conclusions. Costs for NHS hospital contacts will be taken from NHS reference costs[39]. Nationally applicable unit costs will be applied to all community health and social care contact. Costs for contacts with the criminal justice system and for criminal activity will be drawn from Home Office estimates[40]. These estimates are made up of three components: the costs in anticipation of crime; as a consequence of crime; and in response to crime.

11.2 Cost-effectiveness analysis

All economic analyses will be carried out on an intention-to-treat basis using a statistical analysis plan drawn up prior to the analysis of the data. Analyses will compare the cost and cost-effectiveness at the final 36 weekfollow-up of XR-NTX versus placebo and XR-NTX versus O-NTX, in line with the primary aims of the study. Additional analyses will explore XR-NTX versus O-NTX versus placebo in a three-way comparison. The primary analysis will explore cost-effectiveness in terms of quality adjusted life years to provide evidence suitable for comparison across disease areas. Secondary analysis will explore cost-effectiveness in terms of the primary clinical outcome measure as a check

on the results of the primary analysis. Cost-effectiveness will be assessed through the calculation of incremental cost-effectiveness ratios, defined as the additional costs of one intervention compared with another, divided by the additional effects of one intervention compared with another.

Uncertainty around the cost and effectiveness estimates will be represented by cost-effectiveness acceptability curves. A joint distribution of incremental mean costs and effects will be generated via bootstrapping to calculate the probability that each of the treatments is the optimal choice that a decision-maker might be willing to pay for a unit improvement in outcome.

Cost-effectiveness acceptability curves will be presented by plotting these probabilities for a range of possible values of the ceiling ratio[41]. In addition, one-way sensitivity analysis will be used to explore the impact of hypothesized variations in the price of XR-NTX. It is anticipated that single imputation using multiple regression will be used for missing total cost data and last value carried forward conservatively employed for missing EQ-5D 5L data, since previous studies of this kind have demonstrated very low rates of missing data (around 5% of the sample in our group's trial of injectable diamorphine maintenance treatment[42]). However, this assumption will be checked, and alternative methods employed, if necessary.

12. Statistics

The trial will be double blind. Active and placebo oral medication will be produced and encapsulated identically. Active and placebo implant devices will be produced and packaged identically. Clinicians and research workers completing baseline, clinic attendance assessments and all follow-ups will be blind to group allocation, as will patients and pharmacists. This design will ensure that the study has a high level of both treatment integrity (delivery of the treatment as intended) and treatment differentiation (treatment conditions differed from one another in the intended manner)[43].

12.1 Power calculation

Estimated treatment effect size and retention to guide the required number of participants for NEAT was based on best available trial evidence and meta-analysis. The trial is designed to compare the effectiveness of extended-release naltrexone (XR-NTX) and oral tablet naltrexone (O-NTX) on an intention-to-treat basis at 12 weeks post-randomisation. There are two comparisons: XR-NTX vs. placebo, and XR-NTX vs. O-NTX. Based on a 2007 HTA systematic review and the naltrexone depot trial by Professor Sandra Comer and her colleagues in the USA[44], the following assumptions were made:

A. The mean percentage of heroin-free urine drug screens at 12 weeks post-randomisation will be approximately 0.30 (30%) in the placebo and O-NTX treatment arms, respectively, and 0.55 (55%) in the XR-NTX treatment [45]
B. The standard deviations of the treatment groups will be of a similar magnitude [46]We estimate the common standard deviation to be 30.
C. The minimal clinically significant difference between the XR-NTX and O-NTX / placebo group will be a 25 point difference in percentage observable at 12 weeks post-randomisation, equating to an effect size of 0.8.
D. An expected 40% attrition rate based on previous trial data[47].
E. To control for multiple comparisons in the primary analyses, Bonferroni correction has been applied to the significance level reducing it by a factor 2. Thus the significance level will be considered at 2.5%.

12.2 Estimated required sample size

With an anticipated 0.8 effect size, a common standard deviation of 30, expected attrition at 40%, and testing significance at 2.5%, a sample size of 300 participants randomized on a 1:1:1 basis to the three arms (100 participants in each arm) will have 98% power to detect a 25 point difference in the percentage heroin-negative urines for the planned comparisons of active treatment arm XR-NTX vs. placebo and active treatment arm XR- NTX vs. standard oral treatment O-NTX.

12.3 Randomisation

The King's Clinical Trials Unit will oversee randomization. Recruiting centre research staff will randomize participants to one of the three arms of the study (ratio 1:1:1), stratifying by clinical centre, prison or community referral, and recent cocaine use (yes or no) using randomly varying block sizes, via the online randomization system based at King's CTU.

12.4 Analysis

A comprehensive statistical analysis plan will be be developed and agreed with the trial's oversight committees.

There will be no planned interim analyses. An analysis of the data will be conducted once the trial database has closed. The Data Monitoring Committee will collate effectiveness and safety data during the trial to inform their recommendations to the Trial Steering Committee. A mid-trial formal data analysis is not envisaged.

Statistical analysis will be by intention-to-treat. Descriptive analyses (Q-Q plots, means and standard deviation, median and IQR, or numbers and proportions as appropriate) will be performed for the baseline variables and outcome variables, and will be described by treatment group. The time-to-event outcomes will be explored using life tables and survival plots (Kaplan-Meier curves).

The primary outcome analysis for the effectiveness of XR-NTX vs. placebo, and XR-NTX vs. O-NTX is described in Section 9.1. The secondary outcome analyses are described in Section 9.2.

In the case of missing assessments, such analysis can include these participants provided that pre-randomisation values are available for the respective scales. The analysis presumes that the drop-out mechanism is missing at random (MAR). We will examine the scope for using multiple imputation (MI) to generate complete data records as a means of achieving greater efficiency and reduced missing data bias. We will also include as covariates in both model and MI any variables found to be associated with drop-out.

The significance level will be 2.5% (two-sided) for the primary outcome analysis and 5% (two-sided) for secondary outcome analysis. Group difference estimates and associated confidence intervals will be reported. The trial statistician will remain blind whenever possible until the main analyses have been completed.

Loss to follow-up, departures from randomized treatment and the prevalence of serious adverse events will be reported at 12, 16, 24 and 36 weeks post randomization.

13. Trial Steering Committee

A Trial Steering Committee (TSC) and a Data Monitoring Committee (DMC) will operate independently from the Trial Management Group (TMG), the study funder (NIHR/HTA), and the Co-sponsors (King's College London & South London and Maudsley NHS Foundation Trust). The operation of each group is summarised as follows:

The TSC's key purpose will be to ensure the overall integrity of the study; monitoring its progress; investigating any serious adverse events; and taking account of regular reports from the DMC and

TMG. Ultimate responsibility for any decision required on the trial's continuation will lie with the TSC. The Committee will consist of an independent Chair (Professor of Addiction Psychiatry or Psychology), and four other members:

- A Patient and Public Involvement representative;
- A Senior Manager from Public Health England;
- An NHS addiction service commissioner;
- A healthcare treatment provider;

There will also be three overseas members: Professors Evgeny Kruptisky (University of St. Petersburg, Sandra Comer (University of New York) and Professor Walter Ling (University of California Los Angeles). These external members have been costed to attend the London centre for one visit each and we will invite their participation at other meetings via teleconference.

The TSC's membership will be approved by the Sponsor, and will reflect all relevant disciplines. TSC meetings will be attended by the Chief Investigator (JS), Lead Investigator (JM), at least one PI (ED, MK or SM), KCTU Manager (CM), Trial Statistician (JH) and Trial Manager (TBA, secretary to the TSC). The co-sponsor representative (TBA) will be invited to observe each meeting. The TSC is expected to meet six times across the study (or more often, if determined by the Chair.

14. Data Monitoring Committee

The DMC's key purpose will be to monitor the trial data to ensure that it is being implemented in accordance with the highest standards of patient safety and ethical conduct. Throughout the trial, the Committee will monitor data on recruitment, adverse events, emerging external evidence, sample characteristics and primary outcomes and make recommendations if any interim analysis is required.

The DMC will consist of an independent Chair (a senior clinician with expertise in addiction pharmacotherapy trials) and three other members: a university based trials statistician not involved in the study; a treatment provider; and a Patient and Public Involvement representative.

The DMC's membership will be approved by the Sponsor. DMC meetings will be attended by the Chief Investigator (JS), Lead Investigator (JM), KCTU Manager (CM), Trial Statistician (JH) and Trial Manager (TBA, secretary to the DMC). The DMC will meet six times on the same Study Month schedule as the TSC.

15. Trial Management Group (TMG)

The TMG will be responsible for the trial's day-to-day running and management. Chaired by the Chief Investigator (JS) or the Lead Investigator (JM), the membership will include: all investigators; the KCTU Manager (CM); Trial Statistician (JH); Health Economist (SB); Trial Manager (TBA, Secretary to the TMG); Data Manager (JK); and a Patient and Public Involvement representative. The TMG will oversee the development and operation of the study, monitor and maintain recruitment rates, and devise any necessary workarounds that may arise in patient management or the conduct of the trial, ensure that all required financial, insurance and indemnity arrangements are instigated, organise site agreements between each of the three clinical centres and the Study Office and draw up the study publication policy and strategy. The TMG will be divided into three work-streams to oversee: the development of the study protocol and assessments; the trial database; and writing papers. These sub-committees will be appointed by the full TMG and will meet as necessary.

16. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Co-Sponsor(s), Regulators and REC direct access to source data and other documents (eg patients' case sheets, blood test reports, histology reports etc).

17. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to London Dulwich Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Co-sponsor), the REC and the MHRA within the timelines defined in the Regulations.

In relation to the study's registration and adoption: an MHRA Clinical Trial Authorisation application will be made. NEAT has been registered with EudraCT and will be registered with clinicaltrials.gov, a publicly accessible database, before participant recruitment. The Co-sponsors will be King's College London & South London and Maudsley NHS Foundation Trust and the research team will apply for adoption by the Mental Health Research Network.

18. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

The trial will incorporate a range of data management quality assurance functions. As the data are entered online, the Data Manager will log any queries generated and feed these back to the centre research workers in a timely manner. Maintaining a single point of contact between each centre and the KCTU, the KHP-CTO CRA will conduct regular monitoring visits at each centre. Any necessary alterations to entered data will be indicated clearly with an audit trail from the original point of data entry, to ensure that any such amendments, and the reasons for them, can be inspected and tracked. KHPCTO will undertake, on behalf of the Sponsor, independent administrative audits of the trial master file and monitoring at all sites and pharmacies periodically during the trial to ensure compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its subsequent amendments.

18.1 Quality assurance of the psychological intervention

The following procedures will ensure and document the integrity and fidelity of the behavioural interventions.

- Preparation of manuals for the behaviour therapy to incentivize clinic attendance and the mapping-based care planning and task-setting case management model. These materials will be web-accessible as part of the publication of study reports;
- Standardized delivery of these interventions achieved through a staff training programme organized during the preparatory phase, and supplemented by routine clinical supervision;
- A Session Record form which will be completed by the patient and therapist to provide a summary of the methods used in each session; and

- With consent from the patient, 12 weekly key work sessions (including those focusing on mapping, task setting and relapse prevention) will be audio recorded.
- These digital files will be stored securely as part of the study record.
- As these are collected, one of the four session recordings in each of the 3 months will be randomly selected and rated independently for detailed fidelity analysis.

Adapted from a protocol the NEAT team has developed for a behaviour therapy trial in opioid agonist maintenance therapy, these will be rated for protocol adherence by an independent clinician. Any departure from the protocol in terms of content or style of interaction will result in further supervision.

19. Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

Patient data will be anonymised.

- All anonymised data will be stored on a password protected computer.
- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the KHP-CTO Archiving SOP.

Centre PIs will ensure that all personnel are familiar and comply with these guidelines. Data management procedures for the trial will be developed and overseen by the King's Clinical Trials Unit.

19.1 Data collection

Baseline data will be collected and entered by researchers in each study site prior to randomization. Each participant will be assigned a unique trial ID number via the InferMed MACRO eCRF system hosted at the KCTU at the start of the assessment process. This number will be written on all clinical assessment forms, datasheets and databases used to record participant data. Trial data will be first entered on to paper source datasheets provided to each centre during the preparation phase. The research team will endeavour to minimise the use of paper at all times. A hard copy of a record sheet linking patient identity, contact details and trial ID number (including medication pack number) for all participants will be kept at each site. This will be placed securely in a locked filing cabinet separate from datasheets. All data will be kept secure at all times and maintained in accordance with the requirements of the Data Protection Act and archived locally according to the KHP-CTO Archiving SOP and the host institution's additional procedures.

20. Data Management

All baseline and follow-up data will be entered on the online InferMed MACRO electronic data capture (EDC) system (infermed.com). This system is regulatory compliant (GCP, 21CRF11, and the EC Clinical Trial Directive). An electronic case report form (eCRF) using the MACRO EDC will be programmed by the KCTU in collaboration with the Trial Manager (TBA), Trial Statistician (JH) and Health Economist (SB), and hosted on a dedicated secure server within KCL.

The eCRF system will have full audit trail, data discrepancy functionality, database lock functionality, and supports real time data cleaning and reporting. The KCTU will provide training, essential documentation, and user support to the study centres, and on-site audit and monitoring.

A detailed Standard Operating Procedure will cover data recording, online entry, checking, central backup and storage. A regularly updated coding manual will be developed to accompany the study database. The Trial Manager will provide usernames and passwords to any new researchers. Only those authorised by the Trial Manager will be able to use the system.

20.1 Database lock

After written recording, each research worker will transcribe data onto the eCRF within one working week of a participant assessment. After completion of all follow-ups and prompt entry of data, the Trial Manager will review the data and issue queries. The research worker must then answer these queries before the participant's data is 'frozen' within the database. After that time, changes will not be made to the database by the centres unless specifically requested by the Study Office in response to statistician data checks. At the end of the trial, the centre PI will review all the data for each participant and provide electronic sign-off to verify that all the data are complete and correct. At this point, all data will be formally locked for analysis. At the end of the trial, each centre will be supplied with a CD-ROM containing the eCRF data for their centre. This will be filed locally for any future regulatory or internal audit.

21. Publication Policy

A layered communication plan for the lifecycle of the trial will be developed to communicate material in the best format to our audiences (including service users; family members; policy makers; treatment commissioners; the general public; and scientific peers). We will: (i) report quarterly on progress to each of the three clinics' Service User Forums; (ii) produce an annual trial newsletter (MHRN to disseminate); (iii) seek to describe our work at MHRN hub conferences; (iv) seek MHRN support for a conference in the last quarter of the study as part of our dissemination work; and (v) produce results and practice briefings for Public Health England and national stakeholder audiences. This collective activity will support the communication of results via general medical journals.

22. Insurance / Indemnity

Insurance for claims relating to the study design and co-ordination will be provided by KCL. NHS indemnity for study sites will be available.

23. Financial Aspects

Funding to conduct the trial is provided by the National Institute for Health Research Health Technology Assessment program.

24. Time Table

The NEAT Trial will be completed over 45 months. The study will start in September 2014 and first patient will be enrolled in November 2015. The study will end in May 2018. In each of the two clinical recruitment centres, 1 participant will be recruited each week with recruitment of the 300 participants completed in 104 weeks.

There will be four phases: preparation, participant recruitment, and analysis, as follows.

NEAT phase	Activity	Study month	Start date	End date
I	Preparation	1-11	09/14	08/15
II	Recruitment	12-32	09/15	04/17
III	Follow-ups	15-40	12/15	12/17
IV	Analysis and final reporting	41-45	01/18	05/18

The project timetable and milestones are summarised as follows:

Contract start date 1st September 2014 (45 months total duration)

August 2014	CTA application to MHRA with Manufacturer's IB and IMP dossier
February 2015	Joint TSC/DMC meeting
April 2015	Employ trial manager
August 2015	Seek all R&D approvals Place IMP purchase and placebo manufacture orders Prepare study specific process documents Test and signoff eCRF system Study site staff training
September 2015	Conduct site initiation visits at all sites IMP delivery to all sites First patient enrolled
February 2016	Annual progress report to DMC, NIHR and MHRA
July 2016	DMC and TSC meetings Annual safety report to MHRA Annual progress report to ethics
January 2017	DMC and TSC meetings
February 2017	Annual progress report to DMC, NIHR and MHRA
April 2017	All sites end recruitment
July 2017	DMC and TSC meetings Annual safety report to MHRA Annual progress report to ethics
December 2017	Field-work (follow up) completed
January 2018	Site close out visits Database lock Primary analysis begins

May 2018	Analysis complete HTA report submitted Primary paper submitted for publication

25. Learning lessons from the closure of the NEAT trial: qualitative follow-up

Difficulties recruiting to randomized controlled trials (RCTs) are common within medical research (Treweek et al., 2010; Watson & Torgerson, 2006) and have also been documented within addiction research (Ashery & McAuliffe, 1992; Demaret et al., 2014; Melberg & Humphreys, 2010; Oviedo-Joekes et al., 2015; Thomson et al., 2008). For example, a review of RCTs across a range of medical conditions found that nearly half received an extension due to recruitment problems (Sully et al., 2013). Addiction RCTs will encounter recruitment challenges similar to other medical RCTs (Thomson et al., 2008), but seem likely to face additional 'specific' difficulties. As various authors have already documented (Andreasson et al., 1990; Ashery & McAuliffe, 1992; Blanken et al., 2010; Oviedo-Joekes et al., 2015; Thomson et al., 2008), these potentially relate to:

a) patient factors (e.g. barriers to attending appointments and services, lack of understanding about research, low motivation for treatment, concerns about being assigned to a placebo treatment, less patients in particular areas than expected, patient mobility creating difficulties contacting patients)
b) service factors (e.g. very high staff workloads and limited clinic capacity, staff scepticism about new treatments, concerns about patients leaving successful treatments to participate in the RCT, limited research culture in the recruitment setting)

In consequence, it may be necessary to build a range of strategies into addiction RCT designs to facilitate and increase recruitment. These might, for example, include financial reimbursement/ incentives (Free et al., 2010; Martinson et al., 2000), simplified referral processes (Ashery & McAuliffe, 1992; Thomson et al., 2008), appointment reminders (Ashery & McAuliffe, 1992; Thomson et al., 2008), respondent-driven sampling, where trial recruits recruit further participants from their social networks (Burlew et al., 2011), and significant engagement with peer and community organisations (Burlew et al., 2011; Oviedo-Joekes et al., 2015; NIDA, 2008).

Ultimately, the successful execution of any individual RCT will depend on the characteristics of the study population, other setting and contextual factors, and the intervention being trialled. Nonetheless, the more we understand about the operationalization of trial designs within the addiction field, the more likely we are to complete studies successfully going forwards. In the UK, there is a notable lack

of methodological literature on the design and delivery of addiction-related RCTs, particularly those involving people with very complex drug problems. It is within this context that the Naltrexone Enhanced Addiction Treatment (NEAT) trial was conceived, designed and funded.

The NEAT trial was the result of an HTA-commissioned call to explore the potential clinical value of the new ultra-long-acting forms of naltrexone (implants and depot injections) versus existing oral naltrexone and also versus placebo (to test the ability to prevent relapse to heroin/opioid addiction). The study had the strongest trial design ever applied in the addictions field in the UK: a double-blind, double-dummy, placebo-controlled randomised clinical trial. The research team also had considerable experience of addictions research, including clinical trials. Despite this, there were problems executing the work. Initially, non-cooperation of the naltrexone manufacturer created time delays as a new supplier of both placebo and active implants had to be found. Next, there were organisational problems related to changes in the commissioning process for clinical services. Then, the two main trial sites (South London and Birmingham) failed to recruit participants, despite special attention and added resources.

Although a decision to wind down the NEAT trial was made in November 2016, ultra-long-acting naltrexone antagonist medications still need to be studied and they are therefore likely to be the subject of future NIHR/HTA trials. Before commissioning and undertaking any further research on naltrexone, or indeed further clinical research trials in this area, it is important to first learn lessons from the NEAT trial through some in-depth qualitative follow-up.

25.1 Aim

- To learn lessons from the NEAT trial in order to inform the design and conduct of a future successful naltrexone implant trial and to improve current understanding of conducting addiction treatment trials in clinical contexts.

25.2 Objectives

1. To understand factors (patient, contextual and intervention related) that both facilitated and impeded the screening process of the NEAT trial
2. To understand factors (patient, contextual and intervention related) that encouraged or discouraged patients from agreeing to participate in the NEAT trial
3. To understand factors (patient, contextual and intervention related) that both facilitated and impeded progression from agreement to participate in the NEAT trial to actually joining the trial
4. To assess the treatment experiences of individuals who were accepted onto the NEAT trial but did not progress to join the trial

5. To assess the treatment experiences of all individuals who participated in the NEAT trial
6. To explore intended and unintended outcomes of participation in the NEAT trial
7. To ascertain the views and experiences of drug agency staff and research team members about the design and conduct of the NEAT trial
8. To ascertain the views of drug agency staff and research team members about how a future naltrexone trial should be designed and conducted
9. To assess whether the problems encountered were likely to be specific to naltrexone
10. To assess whether the problems encountered were likely to be specific to addiction trials

This follow-up has been designed to be incorporated into the NEAT trial over the period when it is being wound down. As a result, it is subject to a number of constraints. First, speed of data collection will be essential to ensuring that those involved in the NEAT trial can both be successfully located and recall sufficient information about the trial to enable meaningful analyses. Second, the small number of participants successfully recruited onto the trial (n=6) limits the scope of data collection. Third, time delays in securing NHS ethics approval could jeopardise the follow-up. For these practical reasons, it will be necessary to undertake a small exploratory follow-up study. Qualitative research, involving semi-structured interviews with a diverse range of individuals involved in the NEAT trial, provides an ideal method of generating the required data.

25.3 Sampling and recruitment

Participants (n=30) will be purposively sampled from 4 groups associated with the trial:

i. Individuals who were approached about the NEAT trial but did not go on to join the trial (sampled to include those who received information about the trial, failed to achieve abstinence, accepted alternative treatment elsewhere, and never progressed beyond waiting) (n=12)

ii. Individuals who joined the NEAT trial (n=6)

iii. Staff associated with delivery of the NEAT trial (sampled to include those actually involved in the trial and those referring into the trial, and different levels of staff seniority and disciplines) (n=6)

iv. Researchers associated with delivery of the NEAT trial (sampled to include different levels of staff seniority and roles) (n=6)

Since the trial team has contact details for individuals from all four groups, recruitment should be straightforward as long as there is no undue delay in securing ethics approvals.

25.4 Qualitative data collection

All interviews will be conducted in person by a trained qualitative researcher using a semi-structured topic guide. The guides will be designed to address the study aims and objectives.

Patient guides would be tailored to each interviewee sub group, but include such topics as:

- Patient background (e.g. drug use and drug treatment history; prior to, during and post the NEAT trial)
- Views and experiences of the NEAT trial study materials (information sheets, consent forms etc.)
- Views and experiences of the NEAT trial screening process (including any verbal information provided)
- Reasons for agreeing or not agreeing to participate in the NEAT trial (probing for views on naltrexone, implants, placebo, blinding, randomization etc. where possible)
- Views and experiences of the period between screening and participation in the NEAT trial
- Views and experiences of participation in the NEAT trial (probing for views on naltrexone, implants, placebo, blinding, randomization etc. where possible)
- Views and experiences of the NEAT trial closure
- Views and experiences of how participating in the NEAT trial affected any decisions about illicit drug use or the experience of any (re)lapses or produced any other outcomes
- Willingness/ lack of willingness (and reasons) to participate in future similar trials in the future

Staff and researcher guides would be tailored to the interviewee sub group, but include such topics as:

- Views and experiences of the NEAT trial study materials (information sheets, consent forms etc)
- Views and experiences of the NEAT trial screening process (including any verbal information provided)
- Views on why patients agreed or disagreed to participate in the NEAT trial (probing for views on naltrexone, implants, placebo, blinding, randomization etc. where possible)
- Views and experiences of the period between screening and participation in the NEAT trial (for patients and staff)
- Views and experiences of participation in the NEAT trial (for patients and staff) (probing for views on naltrexone, implants, placebo, blinding, randomization etc. where possible)

- Views on organisational/ clinic factors that might have affected participation in the trial (e.g. organisational change, competitive tendering, governance issues)
- Views and experiences of the NEAT trial closure (for patients and staff)
- Views and experiences of how participating in the NEAT trial affected patient decisions about illicit drug use or the experience of any (re)lapses or any other outcomes
- Willingness/ lack of willingness (and reasons) to participate in future similar trials in the future (for patients and staff)
- Views on how a future naltrexone trial should be designed and conducted (including such factors as the context/ setting; information provision; screening; randomization; and waiting period between screening and trial entry)

All interviews will be audio recorded and last approximately 45 minutes to one hour.

25.5 Qualitative data management and analyses

All interviews will be transcribed verbatim by a professional transcriber, coded using MAXQDA software, and analysed using Framework (Ritchie & Spencer, 1994). This will enable the identification of expected and unexpected themes and patterns in data and exploration of similarities and differences of opinion and experience by interviewee sub-groups. Findings can then be compared and contrasted with the existing literature on trial recruitment (both in the medical sciences more generally and within the more limited addictions literature). A clear audit trail from the interview data to the findings will be guaranteed by following the stages of Iterative Categorization (Neale, 2016).

25.6 Patient and public involvement

Researchers at National Addiction Centre already work closely with an established Service User Research Group (SURG) when planning and conducting their research: http://www.kcl.ac.uk/ioppn/depts/addictions/research/SURG/index.aspx Group members will be consulted on the study materials, including the content of the topic guides, data collection, data analyses and interpretation. They will also be invited to participate in writing and dissemination activities.

25.7 Outcomes and outputs

The study will generate detailed information on the processes of initiating the trial and the difficulties subsequently encountered that will offer important lessons for the research team, other researchers seeking to undertake similar trials, patients and clinicians who may be approached to participate in similar trials, and bodies (such as NIHR) who may wish to commission similar research in the future.

The study should produce at least one peer reviewed publication, an international conference presentation, and a short summary of the findings.

25.8 Timeline

The qualitative follow up will be completed within six months of securing all necessary approvals.

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26. Signatures

_____ _____

Chief Investigator Date

Professor John Strang

_____ _____

Lead Investigator Date

Professor John Marsden

_____ _____

Statistician Date

Dr Elizabeth Ryan

_____ _____

Principal Investigator Date

_____ _____

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