Clinical trial results:
Naltrexone Enhanced Addiction Treatment (NEAT): A randomised controlled trial of the clinical and cost-effectiveness of extended-release naltrexone and oral naltrexone.

Summary

EudraCT number	2013-002584-25
Trial protocol	GB
Global end of trial date	09 January 2018

Results information

Result version number	v1 (current)
This version publication date	23 March 2019
First version publication date	23 March 2019
Summary attachment (see zip file)	FINAL STUDY REPORT (NEAT publication.pdf)

Trial information

Trial identification

Sponsor protocol code	10/46/01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Professor Sir John Strang, Institute of Psychiatry, Psychology & Neuroscience (IoPPN) , 44 0207 848 5109, john.strang@kcl.ac.uk
Scientific contact	Professor Sir John Strang, Institute of Psychiatry, Psychology & Neuroscience (IoPPN) , 44 0207 848 5109, john.strang@kcl.ac.uk
Sponsor organisation name	South London & Maudsley NHS Foundation Trust
Sponsor organisation address	Bethlem Royal Hospital, Monks Orchard Road, Beckenham, United Kingdom, BR3 3BX
Public contact	Professor Sir John Strang, South Londn & Maudsley NHS Foundation Trust, 44 207848 5109, john.strang@kcl.ac.uk
Scientific contact	Professor Sir John Strang, South Londn & Maudsley NHS Foundation Trust, 44 207848 5109, john.strang@kcl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2018
Global end of trial reached?	Yes
Global end of trial date	09 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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?

Protection of trial subjects:

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.

Background therapy:

Participants are voluntarily seeking opioid antagonist treatment for opioid use disorder.

Evidence for comparator:

not applicable

Actual start date of recruitment	01 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from a well-established specialist NHS outpatient addiction clinic in London between 2015 and 2018

Pre-assignment

Screening details:

1. Is 18 years of age or older.
2. Can demonstrate a verbal understanding of the study patient information material, 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

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A - Active XR-NTX and placebo O-NTX

Arm description:

- 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. .

Arm type	Experimental
Investigational medicinal product name	NALTREXONE IMPLANT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Subcutaneous use

Dosage and administration details:

Naltrexolle Tablet 765mg for Implantation is supplied as a slow release copolymer based fannulation of naltrexone for Implantation. to be administered surgically inserted into the subcutaneous tissues of the inguinal area.

Investigational medicinal product name	PLACEBO TABLET FOR ORAL USE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matched placebo tablet administered orally

Arm title	Group B - Placebo XR-NTX and active O-NTX

Arm description:

- 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. .

Arm type	Active comparator
Investigational medicinal product name	PLACEBO TABLET IMPLANT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo tablet for Implantation to be administered surgically inserted into the subcutaneous tissues of the inguinal area.

Investigational medicinal product name	Naltrexone Hydrochloride 50 mg film-coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Naltrexone Hydrochloride 50 mg film-coated tabletsO 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.

Arm title	Group C - Placebo XR-NTX and placebo O-NTX

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	PLACEBO IMPLANT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo tablet surgically inserted into the subcutaneoustissues of the inguinal area.

Investigational medicinal product name	PLACEBO TABLET FOR ORAL USE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matched placebo tablet administered orally

Number of subjects in period 1	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
Started	2	1	3
Completed	2	1	3

Baseline characteristics

End points

End points reporting groups

Reporting group title	Group A - Active XR-NTX and placebo O-NTX

Reporting group description:

- 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. .

Reporting group title	Group B - Placebo XR-NTX and active O-NTX

Reporting group description:

- 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. .

Reporting group title	Group C - Placebo XR-NTX and placebo O-NTX

Reporting group description:

Placebo

Primary: Primary Endpoints

End point title	Primary Endpoints[1]

End point description:

The aim of the NEAT study was to determine the clinical effectiveness and cost-effectiveness of enhanced
naltrexone in the treatment of OUD, with the primary objective of answering the following questions:
1. Is extended-release naltrexone treatment more effective than placebo extended-release naltrexone at reducing heroin use?
2. Is extended-release naltrexone is more effective than oral naltrexone at reducing heroin use?
3. What is the relative cost-effectiveness of extended-release naltrexone and oral naltrexone treatment in
terms of quality-adjusted life-years?
4. Is extended-release naltrexone more cost-effective than oral naltrexone in terms of quality-adjusted life-years gained?

End point type	Primary

End point timeframe:

Duration of trial.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see attachment for full results.

End point values	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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	1	3	
Units: whole	2	1	3	

Attachments (see zip file)	FINAL RESULTS/NEAT publication.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoints

End point title	Secondary Endpoints

End point description:

1. compare treatment retention and medication and psychological intervention adherence rates among the extended-release naltrexone, oral naltrexone and placebo conditions
2. contrast the extended-release naltrexone, oral naltrexone and placebo conditions on quality-of-life indices
3. contrast extended-release naltrexone, oral naltrexone and placebo conditions on:
l heroin and cocaine craving
l self-reported opioid, cocaine, amphetamine and benzodiazepine use (with past 48-hour abstinence verified via UDS)
l alcohol use
l injection health risk behaviours
l psychological health (depression and anxiety symptoms)

End point type	Secondary

End point timeframe:

Duration of Trial

End point values	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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	1	3	
Units: whole	2	1	3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 36 weeks trial duration.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Whole Trial

Reporting group description: -

Serious adverse events	Whole Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Heroin Overdose			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Whole Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)		
General disorders and administration site conditions			
Pain at site of inplant			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2015	Addition of new secondary objective and deletion of a secondary objective. Changes to IMP labelling
15 January 2016	Plasma naltrexone' added to the secondary endpoint summary as it is mentioned in the text of the' plasma monitoring' section later in the protocol but not in the summary. The 'naloxone challenge' was moved from week 1 to randomisation as it was entered in week 1 in error Text was added to the 'Dispensing and distribution' section to allow for emergency issuing of drug. Reference to 'antipsychotics, anticonvulsants, antidepressants and anxiolytics' was removed in the 'Concomitant Medication' section as there is no evidence to support those types of drugs being prohibited medication. The 48 hour minimum time period was removed from Inclusion Criteria 2 The text in Inclusion Criteria 5 'a Morphone 2000 [opioid]' was removed as that type of UDS cup is no longer being used in the study. Exclusion criteria 18 has been amended due to concern of potentially vulnerable patients not having naltrexone to carry them through screening period. Some potential patients will need naltrexone during the screening period as they would have just been released from prison and the normal clinical practice is to give these patients naltrexone so they won't overdose. Exclusion criteria 20 was changed from 'Current (past 30 day) suicidal ideation/plan, or recent (past six months) suicidal ideation or suicide attempt' to 'Current (past 30 day) suicidal planning, or recent (past six months) suicide attempt.' as this is more in line with clinical practice. In the 'Primary Effectiveness Parameters' the analysis model has been changed from an analysis of covariance model to a regression model.
09 May 2016	Change in the language of the exclusion criteria to allow a holding does of naltrexone if there is a length of time between randomisation and the start of treatment. Addition of more detailed statistics section

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

It is not possible to reach firm conclusions from the observations on the small number of study participants
who entered the study. This is a major limitation within this report.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30702059