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Full study title: FORWARDS-1; Evaluating the safety of acute baclofen in methadone-maintained individuals with opiate dependence. An adaptive, single-blind, placebo-controlled ascending dose study of acute baclofen on safety parameters in opioid dependence during methadone-maintenance treatment; a pharmacokinetic-pharmacodynamic study.

Short title: FORWARDS-1; Evaluating the safety of acute baclofen in methadone-maintained individuals with opiate dependence

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Chief Investigator: Professor Anne Lingford-Hughes

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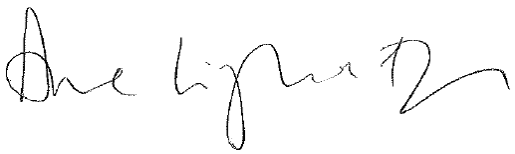
Signature: 

Date: 15 Jun 2021

CONTENTS

1. GENERAL ADMINISTRATIVE INFORMATION

1.1 Protocol Information

This protocol describes the FORWARDS study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

1.1.1 Sponsor

Imperial College is the sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Research Governance and Integrity at:

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1.1.2 Funder

The Medical Research Council (MRC), United Kingdom, fund the study, grant number **MR/T025557/1**.

1.1.3 Peer-Review

The study has been externally peer reviewed and modified through the Medical Research Council Developmental Pathway Funding Scheme (MRC DPFS) Application Procedure, through discussions with independent international reviewers, and through exchanges with the MRC DPFS board.

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1.4 Abbreviations

AE	Adverse Event
AGPs	Aerosol generating procedures
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AUDIT	Alcohol Use Disorders Identification Test
BDI	Beck Depression Inventory
BMI	Body mass index
BP	Blood pressure
BT	Body temperature
CFR	Code of Federal Regulations
CI	Chief Investigator
C_{max}	Maximum (or peak) plasma concentration
COPD	Chronic obstructive pulmonary disease
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
CRM	Continual Reassessment Method
CTA	Clinical Trial Authorisation
DEQ	Drug Effects Questionnaire
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DOA	Drugs of abuse
DPIA	Data protection impact assessment
DSC	Dose Setting Committee
DSM-5	Diagnostic & Statistical Manual, version 5
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
ETCO2	End tidal CO2
FISMA	Federal Information Security Management Act
FEV	Forced expiratory volume
FVC	Forced vital capacity
FTND	Fagerstrom Test for Nicotine Dependence
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation (UK)
GMP	Good manufacturing practice
GP	General Practitioner
HIV	Human Immunodeficiency Virus
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
HRA	Health Research Authority
ICHNT	Imperial College Healthcare NHS Trust
ICRF	Imperial Clinical Research Facility
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
LSEQ	Leeds Sleep Evaluation Questionnaire
LOC	Level of Consciousness
MHRA	Medicines & Health Care Products Regulatory Agency
MINI	Mini International Neuropsychiatric Interview
MRC	Medical Research Council

NEWS2	National Early Warning Score (version 2)
NIHR	National Institute for Health Research
NIMP	Non- Investigational Medicinal Product
OCDUS-H	Obsessive Compulsive Drug Use Scale—Heroin/opiates
OST	Opioid substitution therapy (methadone)
PD	Pharmacodynamic
PK	Pharmacokinetic
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDS	Severity of Dependence Scale
SHAS	Subjective high assessment scale
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SpO_2	Oxygen saturation
SPSS	Statistical Package for the Social Sciences
SSAI	Spielberger State Anxiety Inventory
SSAR	Suspected Serious Adverse Reaction
STAI	Spielberger Trait Anxiety Inventory
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Elimination half-life
TLFB	Time Line Follow Back
T_{max}	Time to reach C_{max}
TMG	Trial Management Group
TSC	Trial Steering Committee
UDS	Urine Drug Screen
VAS	Visual analogue scale
WTAR	Wechsler Test of Adult Reading

2. BACKGROUND

2.1 The problem and unmet need: the challenge of opiate addiction and the need for new treatments

2.1.1 The burden of opiate addiction

Opiate addiction is a major health challenge, its adverse impact on health and social wellbeing clearly evident with death rates rising to record levels (Office for National Statistics, 2018). It is estimated that opioid dependent individuals face mortality risks that are 6–20 times higher than the general population with about half of any cohort of opioid users dying before they reach 50 (Darke et al., 2011; Degenhardt et al., 2011)

Heroin is the most common illicit drug for which people seek treatment. The harm minimisation approach to treatment with opiate substitution medication (OST) and psychosocial support has been highly effective, but there is now an increasing focus on achieving abstinence (UK Home Office, 2017). Indeed abstinence is likely to be better for overall health, particularly in the aging opiate addict population who have been receiving long-term OST and 'have increasingly complex health and social care needs' (Advisory Council on the Misuse of Drugs, 2016). Chronic opioid exposure is associated with impaired respiratory function, lethal disorders of sleep, cardiovascular disorders and impaired immune function, particularly when comorbid with HIV (Stenbacka et al., 2010). Chronic opioid exposure is also associated with impaired cognitive functioning such as inhibitory control, verbal working memory, cognitive impulsivity and cognitive flexibility, as well as in decision-making, emotional and reward processes (Baldacchino et al., 2017).

2.1.2 Opiate substitution therapy and other treatments

Large numbers of individuals receiving OST benefit considerably from their treatment and do not detoxify. Many opiate addicts desire and would benefit from abstinence, but find this hard to achieve and maintain. Opiate withdrawal can be difficult to tolerate due to disturbed sleep, anxiety and craving. These problems may persist into abstinence, increasing the risk of relapse.

Slow tapering of opiate substitute treatment (OST) can attenuate symptoms during withdrawal. Alternatively, during detoxification, a range of prescribed adjunctive medications may be used to ameliorate symptoms, including hypnotics, sedatives or α2 agonists (lofexidine), but their efficacy is limited and/or can only be used short-term. Medications for symptomatic relief are associated with tolerance/abuse liability (Z-drugs, benzodiazepines, pregabalin), significant hypotension (clonidine) or are contraindicated in women of child-bearing age (valproate). Lofexidine was previously prescribed to assist with detoxification, but it remains unavailable in the UK, exposing an unmet need. With this loss of lofexidine, this is now even more crucial to develop a non-opioid approach to detoxification. This is particularly relevant when opioid dependence is uncertain since giving opioids can be dangerous (e.g. respiratory depression) or impracticable (e.g. in custody).

Overall, outcomes for successful detoxification are therefore poor with a minority (30%) of heroin users who enter treatment achieving stable abstinence in 10 to 30 years (Hser et al., 2015). There is therefore a great unmet need for new treatments. Until recently,

research into improving evidence-based pharmacological management of opiate detoxification has therefore been very limited and more is urgently needed.

2.2 The promise of baclofen

Based on preclinical (Phillips & Reed, 2014) and clinical evidence (see later sections 2.3 and 2.4), we propose that the GABA-B agonist, baclofen, has the desired properties to facilitate opiate detoxification and prevent relapse to opiate dependence. Baclofen is a generic medication that is currently licensed for spasticity and is well tolerated (Simon & Yelnik, 2010). It is prescribed off-label to treat alcoholism, such that rapid expansion and adoption by addiction services would be possible if trial outcomes of safety and efficacy in this indication are favourable.

Evidence suggests baclofen will target dysregulated neurobiology during opiate withdrawal like lofexidine but also target anxiety, muscle aches, insomnia, and craving (Agabio et al., 2013). There is also data available from a small number of trials suggesting possible efficacy in supporting opiate withdrawal (Ahmadi-Abhari et al., 2001; Akhondzadeh et al., 2000; Krystal et al., 1992). If shown to be safe in combination with methadone, baclofen can be taken as an adjunct during detoxification and has potential to be continued into abstinence for relapse prevention in a community setting.

2.3 Baclofen- clinical evidence for effectiveness and safety in alcohol dependence

The majority of trials of baclofen outside of its licensed indication of spasticity have been in alcoholism, with far fewer in other addictions. In alcoholism, two meta-analyses have both concluded baclofen is efficacious with “higher rates of abstinence” compared with placebo (Rose & Jones, 2018) and that greater efficacy is seen with doses ≤60mg/d than with higher doses (Pierce et al., 2018). A third meta-analysis however found no superiority of baclofen over placebo on the primary outcomes of each study, though abstinence was not the only outcome assessed here (Bschor et al., 2018). There has been debate regarding baclofen’s dose range, safety and indications (eg drinking vs abstinence) in treating alcoholism. The CI (Lingford-Hughes) and study manager (L Paterson) were members of an international consensus group which produced guidelines to address these issues regarding the use of baclofen to treat alcoholism (Agabio et al., 2018). There is also evidence in a small number of patients that baclofen may reduce acute symptoms of alcohol withdrawal (G. Addolorato, F. Caputo, E. Capristo, L. Janiri, et al., 2002; Addolorato et al., 2003). Further, GABA-B PAMs are also regarded to have potential for treating alcohol use disorder based on preclinical evidence (Augier, 2021; Maccioni & Colombo, 2019).

In cocaine addiction, baclofen blunts limbic activation associated with salient drug cues (Franklin et al., 2011; Young et al., 2014) and whilst baclofen (60mg/d) showed promise in reducing cocaine use in heavier users (Shoptaw et al., 2003), a larger follow-up study failed to show that baclofen helped achieve abstinence (Kahn et al., 2009). The authors queried whether baclofen doses needed to be higher to treat addiction than for spasticity.

Preclinical work continues into developing positive allosteric modulators of GABA-B to treat a range of disorders including addiction (cf Addex partnership with Indivior and

NIDA; https://www.globenewswire.com/news-release/2019/02/14/1725152/0/en/Addex-and-Indivior-to-Accelerate-Additional-GABAB-PAM-Compounds-for-Addiction-as-Indivior-Elects-to-Stop-Development-of-ADX71441.html
https://www.globenewswire.com/news-release/2020/11/02/2118115/0/en/Addex-Receives-Additional-2-8-million-from-Indivior-and-Extends-GABAB-PAM-Research-Collaboration.html

2.4 Baclofen- clinical evidence for effectiveness in opiate withdrawal

Many opiate addicts find detoxification and early abstinence challenging due to presence or fear of withdrawal symptoms including anxiety, insomnia, muscle aches, restless legs and craving that are prominent features of withdrawal. Clinical evidence suggests that such symptoms are likely to be improved by baclofen. In clinical studies, baclofen has demonstrated efficacy in relieving anxiety (G. Addolorato, F. Caputo, E. Capristo, M. Domenicali, et al., 2002; Breslow et al., 1989; Drake et al., 2003; Garbutt et al., 2010; Krupitsky et al., 1993), sleep disturbance (Orr et al., 2012) and restless legs (Mackie et al., 2017; Sandyk et al., 1988), as well as its known efficacy in its licensed indication for muscle spasms. Pre-clinical evidence of efficacy in animal models of opiate dependence include decreased self-administration of heroin, antagonism of conditioned place preference (CPP) to morphine, reduction in stress- and drug-induced reinstatement of opioid CPP and attenuation of morphine withdrawal in response to baclofen (for review see Phillips & Reed, 2014). Clinical evidence of its efficacy in alcohol and cocaine dependence (see above), coincides with some small-scale studies investigating the potential efficacy of baclofen in opiate dependence.

A lab-based study showed that baclofen (40mg, 60mg) attenuated 'relatively mild' opiate withdrawal symptoms from reducing or not taking methadone (66.4±23mg) (Jaffe et al., 1982). Another study investigating cocaine addiction recruited some (Bagley et al., 2005; Bagley et al., 2011) participants taking methadone (70-140mg/d)(Haney et al., 2006). Whilst baclofen's (30mg/d, 60mg/d) effects on cocaine-related outcomes were equivocal, no safety issues arose. Further evidence comes from two clinical trials in opiate withdrawal and one in relapse prevention. An open-label inpatient study found that baclofen (mean:68+13mg/d) improved opiate withdrawal after abruptly stopping methadone (15-25mg/d) in 2 of 5 participants and was well tolerated (Krystal et al., 1992). Further, Krystal concluded that baclofen may have a role as an adjunct in managing opiate withdrawal though noted it did not meet their expectation in treating clonidine-resistant symptoms and that higher baclofen doses may be required to suppress withdrawal symptoms. In an Iranian study of addicts withdrawing from illicit opiate use, baclofen alone (≤40mg/d) compared favourably with clonidine in improving 'mental' and physical withdrawal (Ahmadi-Abhari et al., 2001; Akhondzadeh et al., 2000). Treatment retention and drop-out rates were equivalent (~50%). The majority of participants reported no side-effects. In abstinence, a relapse prevention study reported that baclofen (60mg/d) showed no benefit in opiate-positive urinalysis but some improvements in treatment retention and symptoms (Assadi et al., 2003). No particular safety concerns were raised in these studies.

The full extent of studies of baclofen in opiate dependence are summarised below in Table 1. Comparative details of our proposed proof-of-concept efficacy study that would follow on from successful completion of this safety trial is given in the final column.

Table 1: Clinical trials in opiate addiction compared with our proposed efficacy study, FORWARDS-2.

Study	Krystal 1992	Akhondzaheh 2000 & Ahmadi-Abhari 2001	Assadi, 2003	FORWARDS-2
Country	US	Iran	Iran	UK
Number	5	62	40	56
Setting	Inpatient	Unclear	Outpatient	Outpatient
Design	Open	RCT	RCT	RCT
Treatment stage	Detoxification: methadone stopped abruptly	Detoxification: stopped illicit use; no OST	Relapse prevention after opiate detox	Detox: reduction in methadone ≤12 weeks
OST and dose	Methadone 21 ± 4.2 mg/day	None	None	Methadone, from study 1
Baclofen	Alone	Alone	Alone	Adjunct
Baclofen dose: (divided doses)	68.0 ±13mg/d; (max ≤80mg/d	40mg/d	60mg/d	≤90mg/d
Comparator	None	Clonidine	Placebo	Placebo
Outcome	2/5 participants completed baclofen protocol; completers had less opiate withdrawal	Baclofen showed promise treating 'physical and mental' symptoms	Baclofen resulted in better treatment retention, less withdrawal, depressive symptoms but not fewer +ve opiate urines	
Side-effects, adverse events, safety.	No information about how these were evaluated though stated " 80 mg/day was tolerated without evidence of side effects in this group of patients". "baclofen seemed remarkably benign", with an absence of sedation or hypotension (unlike clonidine)	Not described	Adverse events were assessed systematically with a designed score sheet. No pts in either of the treatment groups reported adverse effects that required dose reduction or termination from the study; no statistically significant differences in adverse effects were found btw the 2 groups	We will systematically assess side-effects, adverse event and safety

2.5 Rationale for the study

Our targeted need is to facilitate opiate detoxification to improve outcomes for those opiate addicts who are on OST but want to be opiate-free. Whilst the evidence from the trials of baclofen-assisted detoxification in opiate dependence are supportive and showed no particular safety concerns, their target population differs from that within the

UK, where typical community detoxification involves gradual OST reduction over the course of 12 weeks or so.

To investigate whether baclofen facilitates opiate detoxification, we must first establish that baclofen can be used safely in a typical UK population of opiate addicts undergoing community-based detoxification.

As baclofen and the most common opiate substitute treatment, methadone, are CNS depressants, we must determine what dose of each is safe to co-prescribe, particularly as patients may take other CNS depressants that are known to contribute to opiate-related deaths (ACMD, 2016). We also need to assess the abuse liability of baclofen in this vulnerable population given the additional risk posed to the individual and the possibility for diversion.

Of primary importance is safety, i.e. what dose of baclofen is safe to co-prescribe with methadone, however we also wish to minimize the potential issue of dose uncertainty in opiate addiction, by determining safety parameters alongside assessing GABA-B system sensitivity in our target population.

Therefore, the following additional important factors must be considered:

1. The potential for CNS depressant effects of combining baclofen and methadone, in particular, the potential for interaction to cause respiratory depression, marked sedation and cardiovascular effects.
2. Dose. The range of doses suggested to be most effective in alcoholism (30-60mg/d) are broadly consistent with those administered in the opiate withdrawal studies of baclofen described (40-80mg/d). Therefore we aim for 30mg as a minimum target dose in our indication, but uncertainty exists around the target maintenance dose.
3. GABA-B receptor sensitivity. Related to the above, we have shown that pharmacodynamic responses to baclofen are markedly blunted in alcoholism suggesting possible alterations in receptor function (Durant et al., 2018). The same may also apply in opiate dependence, with potential consequences for dosing and efficacy signal.
4. The potential for abuse liability- if a signal exists, there are particular risks in this vulnerable population of misuse and diversion, and these must be mitigated in any future study.

2.6 Potential for CNS depressant effects- rationale for respiratory measures

There are no formal RCT studies directly assessing the CNS depressant effects of baclofen in combination with opioids. A retrospective cohort study of opioid overdose found a small increased odds ratio for concomitant baclofen use compared with opioid use alone (Li et al., 2020) , however those with substance use disorder were specifically excluded. There are also no specific reports of an interaction between baclofen and methadone specifically, although baclofen has been shown to potentiate opioid effects such as morphine-induced analgesia (Gordon et al., 1995) and fentanyl-induced anaesthesia ((Corli et al., 1984; Panerai et al., 1985) with iv or im dosing). The potential for a mechanistic interaction is plausible due to co-localisation of spinal GABA-B and opioid receptors in lamina II of the dorsal horn, an important site for nociceptive

processing in C fibre primary afferent neurones, although a supraspinal mechanism cannot be ruled out.

Baclofen alone can cause sedation and has been shown to cause respiratory depression at high doses. In alcohol dependence chronic baclofen was found to be associated with increased risk of all-cause hospitalization and mortality, particularly at high doses (>180mg/day, (Chaignot et al., 2018)). Again, those receiving OST were specifically excluded from the analysis.

In other studies of baclofen alone, a case series collected over 5 years identified signs of toxicity in 9 individuals suffering from severe renal impairment after taking a short course of baclofen (Chen et al., 1997). The authors noted that altered consciousness was the major presenting feature and that respiratory depression was relatively uncommon. A more recent observational study has suggested an association between respiratory depression and baclofen use in spasticity with chronic kidney disease, related to increased circulating baclofen levels (Mitsuboshi, 2021). Other studies mentioning incidence of respiratory depression have been in the context of overdose e.g. in adolescents consuming between 60 and >600mg baclofen in a non-lethal 'mass intoxication' (Perry et al., 1998).

Cases of sleep disordered breathing have been reported amongst those taking chronic baclofen e.g. central sleep apnoea in four individuals receiving chronic baclofen for alcohol withdrawal (NB n=3 were taking >150mg daily, (Olivier et al., 2016)), which was subsequently managed by adaptive servi-ventilation or baclofen cessation. In contrast, in a study of susceptible snorers baclofen (25mg) did not alter sleep disordered breathing (Finnimore et al., 1995). Chronic opioid use, including methadone, is also associated with central sleep apnoeas (Correa et al., 2015).

Due to the inherent risks of combining CNS depressant drugs such as baclofen and methadone, and the vulnerability of this patient group, we will seek to understand whether any respiratory, sedative and cardiovascular effects occur following baclofen administration in combination with methadone in a single ascending dose study, incorporating pharmacokinetic-pharmacodynamic measures.

Monitoring of both cardiovascular and respiratory function will occur, and both will be assessed for significant clinical impairment at screening and forms part of the exclusion criteria.

2.6.1 Respiratory depression

Standard clinical practice for measuring respiratory depression involves monitoring for hypoventilation using pulse oximetry and respiratory rate. However, when combined with measures of carbon dioxide partial pressure (pCO_2), this can provide a more sensitive and earlier indicator of respiratory depression. In addition, evidence suggests that individuals with opiate dependence may display hyposensitivity to pCO_2 (Jolley et al., 2015; Tas et al., 2020).

Whilst there is no unified definition of 'respiratory depression' the most well described indicators of significant respiratory depression are as follows:

- Persistent reductions in SpO_2 (e.g. <90% for more than 10 seconds; (Jolley et al., 2015)
- Absence of inspiratory airflow (apnoea) > 30 seconds combined with a sustained fall in SpO_2
- Sustained ETCO2% per breath exceeding 6.5% (Jolley et al., 2015)

- Sustained CO_2 partial pressure increase by 1kPa (normal range 4.7-6.0 kPa)
- Respiratory rate <9/min (from the NEWS2 score)

In the UK, NHS England has adopted the National Early Warning Score (NEWS2), first produced in 2012 and updated in December 2017, which advocates a system to standardise the assessment and response to acute illness. We will use NEWS2 definitions for the thresholds for triggering an urgent ward-based response as our criteria for determining whether a dose-limiting 'toxicity' (DLT) event has occurred following co-administration of baclofen and methadone. This will include monitoring of respiratory rate, oxygen saturation, body temperature, systolic blood pressure, pulse rate and level of consciousness or new confusion (ACVPU; alert, confusion, voice, pain, unresponsive).

2.6.2 Sedation

Sedation is the most common side effect of baclofen, particularly at higher doses. In healthy controls, we observed mild to moderate sedation in a healthy control cohort following acute doses of 60mg and above, but no such sedation in alcohol dependent participants with doses up to 90mg (Durant et al., 2018). We will monitor sedation using the Glasgow Coma Scale, NEWS2 scale and self-reported drug effects (Subjective High Assessment Scale (SHAS) and Leeds Sleep Evaluation Questionnaire (LSEQ) which both include specific items related to sedation.

2.6.3 Cardiovascular effects

Cardiovascular effects are not commonly reported in response to baclofen, except in studies of renal impairment or after very high doses e.g. in overdose (Nugent et al., 1986; Roberge et al., 1994). Evans et al reported a small effect of 80mg acute baclofen to increase heart rate (increase of 10 bpm) and blood pressure (121 to 125 mmHg) at 2 hours post dose, which returned to normal after 6 hours (Evans & Bisaga, 2009). In our acute study, we observed no overall significant effects on heart rate or blood pressure (Durant et al., 2018).

Methadone is reported to prolong QT interval, however there are no reports of QT prolongation following baclofen, therefore there is no indication that they are not safe to use together with respect to QT intervals.

We will monitor QT and cardiovascular parameters for signs of acute change after baclofen administration.

2.7 Dosing considerations- lessons learned from spasticity & alcohol dependence

In prescribing baclofen for alcohol dependence, variability in response and the lack of robust biomarkers to guide the target maintenance dose means that the target dose for an individual is not well characterised. It is therefore titrated up until clinical benefit is achieved. Typically, 30mg daily or above is prescribed, to be taken in 3 divided doses. This minimum target dose of 30mg for this trial is supported by the literature suggesting that baclofen is efficacious in relapse prevention and in the reduction in daily drinking (G Addolorato et al., 2002; G Addolorato et al., 2007; Flannery et al., 2004)

The main dose and titration limiting factor for baclofen is sedation, though this is also variable, with some individuals able to tolerate very high doses. Consequently, high doses of baclofen were in use for some patients in alcohol dependence (≤300mg/d; 10x higher than initial RCT). However, since meta-analyses have since established that

doses ≥60mg are no more effective than lower doses, safety concerns led the French authorities to approve use of baclofen in alcoholism only up to 80mg/d (Inserim et al., 2017). We have no reason to believe that doses over 90mg will be required in opiate dependence, so do not intend to go above this.

2.8 GABA-B receptor sensitivity

Consistent with historical prescribing of high doses of baclofen in alcohol dependence, we previously conducted a pharmacokinetic-pharmacodynamic (PK/PD) study to understand if the pharmacokinetics of baclofen and/or the sensitivity of the GABA-B system itself is altered in alcoholism that might inform what is the optimal dose (Durant et al 2018). We successfully established a protocol using a range of subjective and objective measures as well as an assay to measure plasma baclofen levels in healthy controls (n=12) and abstinent alcohol dependent individuals (n=8), who received single oral doses of baclofen or placebo in a crossover design, suggesting reduced GABA-B sensitivity in alcohol dependence. Preliminary evidence is suggestive of similarly blunted sensitivity in opiate dependence (Volpi et al., 1992). This may contribute to the variability in treatment response, variability in the emergence of side-effects, and may explain the lack of superiority of baclofen over placebo in some studies in alcoholism.

The association between the dose of baclofen, experience of sedation and other pharmacodynamic effects, and the relationship to subsequent treatment efficacy, is currently poorly understood. In addition, baclofen dose is known to be a poor predictor of blood concentrations, adding further heterogeneity to the signal. It is therefore important to develop a better understanding of this dose-response relationship. If we were to demonstrate the safety of baclofen, and proceeded with an efficacy trial using flexible dosing without knowing the PK-PD parameters, this would hamper our ability to titrate effectively. This is important because from clinical experience, individuals require resolution of their difficulties quickly so being able to titrate faster to a maximum dose, as required, will be advantageous.

We will therefore apply a similar PK-PD protocol to assess GABA-B sensitivity in opiate addicts receiving methadone with enhanced measurements to assess safety. Data derived from historical controls who took part in the previous protocol will be used in the current protocol to provide a comparator group. This will empirically test whether our opiate population are similarly more tolerant to baclofen as we found in alcoholism. If similar sub-sensitivity is observed in opiate dependence, this would be highly suggestive that it would also be found in other addictions, such as cocaine, and therefore more broadly inform development of medications targeting GABA-B system in addiction.

2.9 Abuse liability background/rationale

Concerns have been raised about the potential for abuse liability of baclofen (Gahr et al., 2014; Praharaj, 2018), and following reports of ‘liking’ in alcoholic populations. So far, this possibility is not borne out by evidence in RCTs of chronic baclofen in alcohol dependence. Acutely, our own study reported no significant “alcohol-like” or “drunk” effects on the subjective high assessment scale (SHAS) following 60 or 90 mg of baclofen. However on the drug expectancy questionnaire (DEQ), although there were no overall significant effects, there was a suggestion of increased “high” and “liking” effects after the 90 mg dose. Anecdotally, several participants stated that they enjoyed the effects, and likened them to those of opiates or benzodiazepines. This has potential

implications for abuse liability, particularly at higher doses, and requires further study. Another study in heavy social drinkers observed no liking effect, but did report 'good grud effect' and 'evevated mood after 80mg acute baclofen (Evans & Bisaga, 2009).

In other studies, possible evidence of abuse liability of baclofen in alcohol dependence was observed when used in combination with alcohol, but baclofen alone did not result in any measurable change in signal (Farokhnia et al., 2017).

The extent of this possible abuse liability needs to be assessed in the vulnerable opiate population due to a possible risk of misuse, in particular when combined with OST, with the aim to address this in future studies, if an abuse liability signal is detected.

2.10 Study Summary

This study will evaluate the safety of acute baclofen in methadone-maintained individuals with opiate dependence. The goal of the trial is to study the safety of these drugs given in combination using an adaptive, single-blind, placebo-controlled ascending dose design investigating the impact on respiratory, cardiovascular and pharmacokinetic-pharmacodynamic (PK-PD) parameters.

This study will determine the maximum safe dose of baclofen depending on the prescribed dose of methadone. Methadone doses will vary depending on the recruited cohort, but we anticipate an average dose of ~53mg (range 5 to 120mg), based on data from local drug and alcohol services. We are seeking a minimum safe dose of 30mg baclofen in combination with a minimum of 60mg methadone. Findings will be used to inform a subsequent proof-of-concept trial of the efficacy of baclofen. We will investigate each of the four factors of i) safety, ii) dose-response, iii) potential for abuse liability and iv) objective and subjective measures of GABA-B receptor sensitivity, providing clarity on the relationship between these factors. We will include a placebo arm to evaluate the pharmacodynamic effects of baclofen, and to control for expectation effects.

Safety will be established using a Bayesian dose-escalation adaptive model which will be informed by the occurrence of dose-limiting toxicity (DLT) events at increasing doses of baclofen at the following dose levels: 10, 30, 60, 90mg. The evaluation window for all outcomes will begin at dosing and end at 5 hours post-dose, with further follow-up by phone the following day. The DLT of primary concern is respiratory depression, and we consider that the risk increases with the dose of baclofen and methadone-maintenance level. Formally, the objective is to find the combination associated with 15-25% risk of a DLT. The combination-toxicity response will be evaluated using the continual reassessment method (Wheeler et al., 2019), a model-based design for trials that aim to find the maximum tolerated dose, where the baclofen dose recommendation for each given patient with prescribed dose of methadone will be supported by the adaptive Bayesian model. Participants will be randomised (single-blind) to baclofen or placebo in a 3:1 ratio. If allocated to baclofen, participants will be dosed in groups of up to 3, with a maximum sample size of 48 allocated to baclofen, and 16 to placebo.

Outcome measures that will be used to determine the incidence of a DLT will include oxygen saturation, respiratory rate, cardiovascular measures (ECG, blood pressure) and CNS effects (sedation, alertness). End tidal CO_2 and adverse events will also be monitored.

The adaptive Bayesian model will be regularly updated (after each group of up to 3 participants administered baclofen) given the observed patients' responses, providing efficiency in decision-making, by recommending the most likely safe target individualised dose. The study can therefore be stopped earlier for safety if the model suggests that 30mg of baclofen and 60mg of methadone is highly likely to be *unsafe*. The study can also stop earlier if the highest dose of baclofen (90mg) is highly likely to be *safe*, i.e. shows no DLTs with 120mg of methadone, provided that the study has also achieved sufficient data to meet secondary endpoints.

In addition to the approach described above, an evaluation of pharmacokinetic parameters will be investigated through regular blood sampling and assay of baclofen and methadone plasma concentrations. The pharmacodynamic effects of baclofen relative to placebo, and their dose separation will be determined through objective (plasma growth hormone concentrations) and subjective measures (visual analogue scales and questionnaires for drug effects, anxiety, sleep). The potential for abuse liability, relative to placebo, will be assessed using the Drug Effects Questionnaire.

GABA-B receptor sensitivity will be determined through comparison of pharmacodynamic effects in comparison with historical healthy controls, using data derived from previous work using comparable measures and time-points at the 10 and 60mg baclofen dose levels (Durant et al., 2018).

Primary & secondary endpoints: If we find that all dose levels of baclofen are safe up to and including 90mg in combination with 120mg methadone (primary endpoint), the study can still continue up to the maximum sample size to achieve maximum precision for secondary outcomes, explore more methadone doses (<120mg) in a variery of participants and baclofen dose-response separation, as required.

3. STUDY AIMS AND OBJECTIVES

3.1 Study Aims and Objectives:

The primary objective of our programme of research is to establish whether baclofen can facilitate successful opiate detoxification. Due to the inherent risks of combining CNS depressant drugs, we will first determine the safety parameters of taking baclofen in combination with methadone in a single ascending dose study using a Bayesian dose-escalation adaptive model, incorporating pharmacokinetic-pharmacodynamic measures in a randomised, placebo-controlled design.

3.1.1 Primary study objective

1. Aim to determine whether we can safely proceed prescribing a minimum of 30mg baclofen to clients receiving a range of doses of methadone (a minimum of 60mg) through determination of:
    - Lack of CNS depressant activity using measures of respiratory function, cardiovascular function and sedation as follows:
        - Respiratory function (respiration rate, oxygen saturation, end-tidal and/or transcutaneous CO_2)
        - Requirement for intervention (scored according to step-wise algorithm)

- Cardiovascular function (ECG, blood pressure, heart rate)
- Sedation (rating scales, National Early Warning Score- NEWS2, Glasgow Coma Scale)

If clinically significant CNS depressant activity is observed, this will be considered a dose-limiting toxicity (DLT) event (see section 3.4.2 for definition and criteria) and will inform the adaptive model in determining the next dose of baclofen to be administered, according to the next patient's prescribed methadone dose.

Our target dose is for 90mg baclofen to be safely prescribed in those receiving maintenance doses of methadone up to and including 120mg daily. This would provide the full range of prescribing freedom within current guidelines for prescribing of baclofen in spasticity (BNF guidelines, max 100mg/day), and meets recommendations for off-label prescribing in alcoholism (max 80mg/day granted for French temporary license (Rolland et al., 2020), and recommended efficacious doses 30-60mg/day (Agabio et al., 2018). This is also in line with prescribing of methadone as opiate substitution therapy according to Department of Health 'Orange' and NICE guidelines, both of which recommend 60mg/day of methadone as clinical therapeutic target with a maximum of 120mg/d methadone.

Our minimum acceptable dose is 30mg baclofen to be safely prescribed in those receiving maintenance doses of methadone up to and including 60mg daily. Baclofen doses below 30mg/d have not demonstrated efficacy in alcoholism (Agabio et al., 2018), and although the minimum daily recommended doses outlined in Orange and NICE guidelines is 60mg/d methadone, the majority of clients in our services are on methadone doses lower than 60mg/d (average 56.3mg/d), and our target population for those on detoxification or tapering pathways are on even lower doses (i.e. <40mg/day with methadone estimated average of 25mg). Therefore, these 'acceptable minimums' will still capture the majority of clients that we wish to enrol.

3.1.2 Secondary study objectives:

Secondary aims will be investigated and findings used to inform the design of the subsequent proof-of-concept efficacy study 2 and will include:

2. Aim to identify whether there is any evidence of sub-threshold DLT respiratory, cardiovascular or sedation changes in response to baclofen relative to placebo.

Evidence of a sub-threshold DLT changes in response to baclofen would not prevent initiation of further studies in this indication, but would guide prescribing behaviour in subsequent studies.

3. Aim to determine whether there is any evidence of abuse liability signal for baclofen relative to placebo, in combination with methadone, through determination of:
   - Lack of abuse liability as measured by:
     - Drug effects questionnaire (DEQ)

Presence of an abuse liability signal would not prevent initiation of further studies in this indication, but would signal the need for additional monitoring and risk mitigation in future studies.

4. Aim to determine whether there is evidence of reduced sensitivity to baclofen relative to placebo through determination of Subjective drug response (Subjective High Assessment scale, SHAS).

Evidence of a reduced sensitivity to baclofen would not prevent initiation of further studies in this indication, but would guide prescribing behaviour in subsequent studies.

5. Explore the variability in response to baclofen at different baclofen dose levels for (i) CNS depressant activity using measures of respiratory function, cardiovascular function and sedation, (ii) abuse liability measured by DEQ and (iii) subjective drug response (SHAS)
6. Explore the variability in response to baclofen at different methadone levels for (i) CNS depressant activity using measures of respiratory function, cardiovascular function and sedation, (ii) abuse liability measured by DEQ and (iii) subjective drug response (SHAS)
7. Explore the variability in response to baclofen by gender for (i) CNS depressant activity using measures of respiratory function, cardiovascular function and sedation, and (ii) abuse liability measured by DEQ and (iii) subjective drug response (SHAS)

3.1.3 Exploratory objectives

Additional exploratory aims will be investigated and include:

8. Aim to determine whether there is evidence of reduced sensitivity to baclofen through determination of:
    a. Objective and subjective pharmacokinetic-pharmacodynamic (PK-PD) responses using the following measures:
        i. Plasma growth hormone levels
        ii. Plasma baclofen levels
        iii. Plasma methadone levels
    b. The following measures are also to be compared with those of historic controls and those with alcohol dependence (Durant et al., 2018).
        i. Subjective drug response (Subjective High Assessment scale, SHAS)
        ii. Plasma growth hormone levels
        iii. Plasma baclofen levels
9. To investigate the variability in PK-PD responses to baclofen at different baclofen dose levels
10. To investigate the variability in PK-PD responses to baclofen at different methadone levels
11. To investigate variability in response by; tolerability aspects, demographic factors (e.g. age)
12. To identify possible markers of efficacy of baclofen relative to placebo (e.g. sleep, anxiety, restless legs)

3.2 Study hypotheses:

1) CNS depressant activity

a) We anticipate *no evidence of clinically significant respiratory depression* or cardiovascular changes in doses up to 90mg baclofen in those on daily methadone doses up to and including 120mg.
b) We hypothesise that we will observe increased self-reported measures of drug effect, including sedation, with doses at or above 60mg baclofen *relative to placebo*, in combination with methadone doses at or above 60mg.
   - Increased T-SHAS drug effect score relative to placebo, at peak effect (2-3 h following dosing).
   - We hypothesise that signs of sedation in this opiate dependent cohort will be blunted in response to baclofen as compared with historic controls (Durant et al., 2018).
   - Reduced peak subjective response following baclofen administration at doses of 60mg or above.

2) Abuse liability
   a) We hypothesise that we will observe *no indication of abuse liability* of baclofen relative to placebo in combination with methadone.
      - No clinically meaningful change from placebo in DEQ 'liking' or 'want more' subscales.
3) PK-PD measures
   a) We anticipate that opiate dependent individuals will demonstrate lower sensitivity to baclofen as compared with historic controls, as follows:
      - Reduced growth hormone response relative to controls at peak effect (~2h post dose) following 60mg baclofen
      - Reduced sedation response (self-report measures) relative to controls at peak effect (2-3h post dose) following 60mg baclofen
   b) We anticipate that opiate dependent participants will demonstrate a comparable pharmacokinetic profile in response to baclofen as compared with healthy controls and those with alcohol dependence (data from (Durant et al., 2018))
4) We expect that baclofen will reduce anxiety after acute dosing and improve sleep measures during the subsequent night of sleep, compared with placebo.

3.4 Outcome measures

3.4.1 Primary Outcome Measures

Primary outcome: The maximum safe dose of baclofen at which 15-25% of evaluable participants experience a dose limiting toxicity (DLT) for prescribed doses of methadone, where a DLT is defined in section 3.4.2 and is comprised of the following components:

1) Intervention level (0 to 4) as described in section 3.4.3
2) National Early Warning Score (NEWS2), measured at discrete time-points
3) Glasgow Coma Scale (GCS) score, measured at discrete time-points
4) QTc on ECG trace, measured at discrete time-points
5) Measures of respiratory function, measured continuously at discrete time-points
   a) Oxygen saturation (SPO_2)
   b) Respiratory (ventilation) rate
   c) Incidence of apnoea

Definitions of the evaluation window and evaluable participants can be found in sections 3.4.6 and 3.4.7 respectively, and the discrete time-points are given in section 4.3.2.

3.4.2 Definition of dose-limiting toxicity (DLT)

A Bivariate Bayesian Logistic Regression Adaptive Model (see sections 4.4 and 8) will be used to determine whether safety limits are exceeded using one or more of the following outcomes as a 'dose limiting toxicity (DLT)':

1) Situation requiring intervention level ≥4 (section 3.4.3) at any time
2) NEWS2 score >4 or score of 3 in any parameter (threshold for trigger of urgent ward-based response)
3) Measures of respiration with a persistent change in at least one of:
    a) Reduction in SPO_2 [≤91% for more than 30 seconds or >5% reduction in SpO_2 for more than 30 seconds
    b) Reduced respiratory rate (≤8/min)
    c) Absence of inspiratory airflow for >30s combined with a sustained fall in SpO_2
4) GCS score <12
5) Persistent QTc prolongation (>500ms or increase of >60ms; if the initial QTc value at any time-point is prolonged, the ECG should be repeated two more times- with 5 minutes between ECG readings- and the average of the 3 QTc values used to determine DLT).

3.4.3 Stimulus Intervention levels:

If marked sedation or apnoea >30s occurs, the following levels of stimulus intervention will be utilised and scored accordingly (0; no intervention).

1. Indirect noise e.g. door opening, closure, cough etc
2. Interrupt patient with direct speech
3. Touch
4. Unable to rouse patient with touch

Any intervention at level 4 or above will meet criteria for a DLT and a clinical decision will be made as to further action.

In the event of the need for clinical intervention, a crash trolley is available within the Clinical Research Facility, and a crash team is available at Hammersmith Hospital. Naloxone will be available in the ICRF as a rescue medication in the event of respiratory depression requiring intervention.

If further emergency clinical investigation and interventions are required, this will involve transfer to the emergency department at Charing Cross Hospital, via ambulance.

3.4.4 Secondary Outcome Measures

Components of DLT:

- Intervention level (0 to 4) as described in section 3.4.3
- National Early Warning Score (NEWS2), measured at discrete time-points
- Glasgow Coma Scale (GCS) score, measured at discrete time-points
- QTc on ECG trace, measured at discrete time-points
- Measures of respiratory function, measured continuously at discrete time-points:
  a) Oxygen saturation (SpO_2)
  b) Respiratory (ventilation) rate
  c) Incidence of apnoea

Respiratory measures:

These will be investigated at each baclofen dose level, for signs of sub-threshold respiratory depression.

- SpO_2- instances of <92% or of >5% reduction for more than 10 seconds
- CO_2- instances of $ETCO_2$% per breath exceeding 6.5% (Jolley et al., 2015) or a partial pressure CO_2 increase by 1kPa (advice from respiratory physician)
- Respiratory rate- instances of absence of inspiratory airflow for more than 10 seconds or respiratory rate drops <9/min
- Time course of SpO_2, CO_2 and respiratory rate following baclofen dosing, relative to placebo.

Sedation measures:
- T-SHAS score (total score on Subjective High Assessment Scale)
  - Mean Total-SHAS score at peak PD response (2-3h) at each baclofen dose level, relative to placebo
  - Time-course of T-SHAS at each baclofen dose level, relative to placebo

Symptom measures:
- Drug Effects Questionnaire (DEQ)
  - Mean 'Drug liking' and 'want more' scores at peak PD response (2-3h) at each baclofen dose level, relative to placebo
  - Time-course of DEQ scale at each baclofen dose level, relative to placebo

3.4.5 Exploratory Outcomes

Sedation measures:
- T-SHAS score (total score on Subjective High Assessment Scale)- self-rated
  - Mean Total-SHAS score at peak PD response (2-3h) at 60mg baclofen dose level, relative to historical controls
  - Time-course of T-SHAS at each baclofen dose level, relative to placebo

Plasma levels: PK and growth hormone measures:
- Plasma baclofen concentrations
  - Mean peak plasma concentration (2-4h) at each baclofen dose level, relative to placebo
  - Time-course of plasma baclofen levels

    - C_{max} (maximum (or peak) plasma concentration, T_{max} (time to reach C_{max}), $t_{1/2}$ (elimination half-life)
    - Variability in PK parameters by gender
- Plasma methadone concentrations
    - Mean plasma concentration (2-4h) at each baclofen dose level, relative to placebo
    - Time-course of plasma methadone levels
- Plasma [growth hormone (GH)], a surrogate marker of GABA-B receptor function.
    - Mean peak plasma concentration (2h) at each baclofen dose level, relative to placebo
    - Mean peak plasma concentration (2h) at the 60mg baclofen dose level, relative to controls
    - Time-course of plasma GH levels
    - Variability in GH profile by gender

Symptom measures:

- Visual analogue scales for anxiety, craving at each baclofen dose level, relative to placebo
- Sleep measure (LSEQ) at each baclofen dose level relative to placebo
    - Improvement in LSEQ score for 'getting to sleep' and 'quality of sleep' factors, no change in 'awakening following sleep' or behaviour following wake' factors.

Other outcomes: actigraphy, heart rate, blood pressure, body temperature.

Phenotypic measures: demographic (gender, age), clinical (methadone dose), drug & alcohol history, validated questionnaire measures.

These measures will be related to the primary and secondary outcomes to support the validity of the adaptive trial design, estimate variability in the signal across these demographic features, to establish novel relationships or conversely, to control for outlier effects.

3.4.6 Evaluation window

The evaluation window for primary and secondary outcome measures will begin at dosing and end at 5 hours post-dose, with the exception of the 'intervention level' (as defined in the DLT definition) which will begin at dosing and continue until the last follow-up phone call. This call will be conducted the following day, and the window will be extended if the participant is experiencing sedation or other symptoms.

3.4.7 Evaluable patient

An evaluable participant is defined as one who has received study medication and has provided sufficient data to meet the primary endpoint of determining the presence or absence of a DLT, *and* sufficient data relating to the main secondary outcome measures. Whether sufficient data has been obtained for this purpose will be determined by clinical judgement on an individual participant basis.

In the unlikely event that a participant decided to self-discharge themselves after dosing but prior to the end of the 5 hour evaluation window, this participant could be counted as an evaluable patient with no DLTs provided they had completed the 2-3h timepoint and that this self-discharge had occurred within a clinical picture of stable or normalising observations. Attempts to complete the follow-up phone call would be made to confirm absence of DLT as defined by 'intervention level'.

In the event of an inability to acquire sufficient data, as defined above, the decision on whether to include an individual's data in the primary (DLT) or secondary analysis, or whether that individual would be replaced, would be made on a case by case basis.

4 STUDY DESIGN

4.1 Description of Overall Study Design

This will be a single-blind, adaptive, randomised, placebo-controlled ascending dose study of a single dose of baclofen in opiate-dependent individuals stably maintained on methadone. Participants will be randomised in a 3:1 ratio to baclofen or placebo. Participants allocated to baclofen will be dosed in groups of up to 3, with a maximum available sample size of 64 (up to 48 on baclofen and 16 on placebo). An adaptive model will inform the dosage of baclofen for each patient group based on the trial data accumulated to date.

The primary objective is determination of the maximum safe dose of baclofen at which 15-25% of evaluable participants experience a dose limiting toxicity (DLT, defined in section 3.4.2) for prescribed doses of methadone.

Potentially eligible participants will be identified by telephone screening and invited to attend a screening visit at one of the study sites. Following informed consent, this visit will ascertain study eligibility, medical, psychiatric and dependence history, obtain self-report and rater-report questionnaire measures and administer an actiwatch, to be worn until the morning after the experimental visit.

Eligible participants will be enrolled into the study and randomised to receive baclofen or placebo in a 3:1 ratio. The baclofen dose allocation recommendation (10, 30, 60 or 90mg) will be made by the Bayesian adaptive algorithm, based on the participant's prescribed methadone dose level and previous learning accumulated by the adaptive model. The Dose setting committee (DSC) retains the ability to override the alogrithm's dose recommendation if clinically indicated.

Following randomisation, participants will attend the Imperial Clinical Research Facility (ICRF) for a single experimental visit, during which they will consume their usual daily dose of methadone under observation soon after arrival, followed by an acute oral dose of baclofen or placebo approximately 1 hour later, as determined by the adaptive trial algorithm.

Measures of respiratory, cardiovascular, subjective and PK will be obtained periodically for up to 5 hours after baclofen dose.

The following day, participants will receive a follow-up phone call to check welfare and will be required to return their actiwatch via pre-paid envelope, or to their local addiction service, as appropriate.

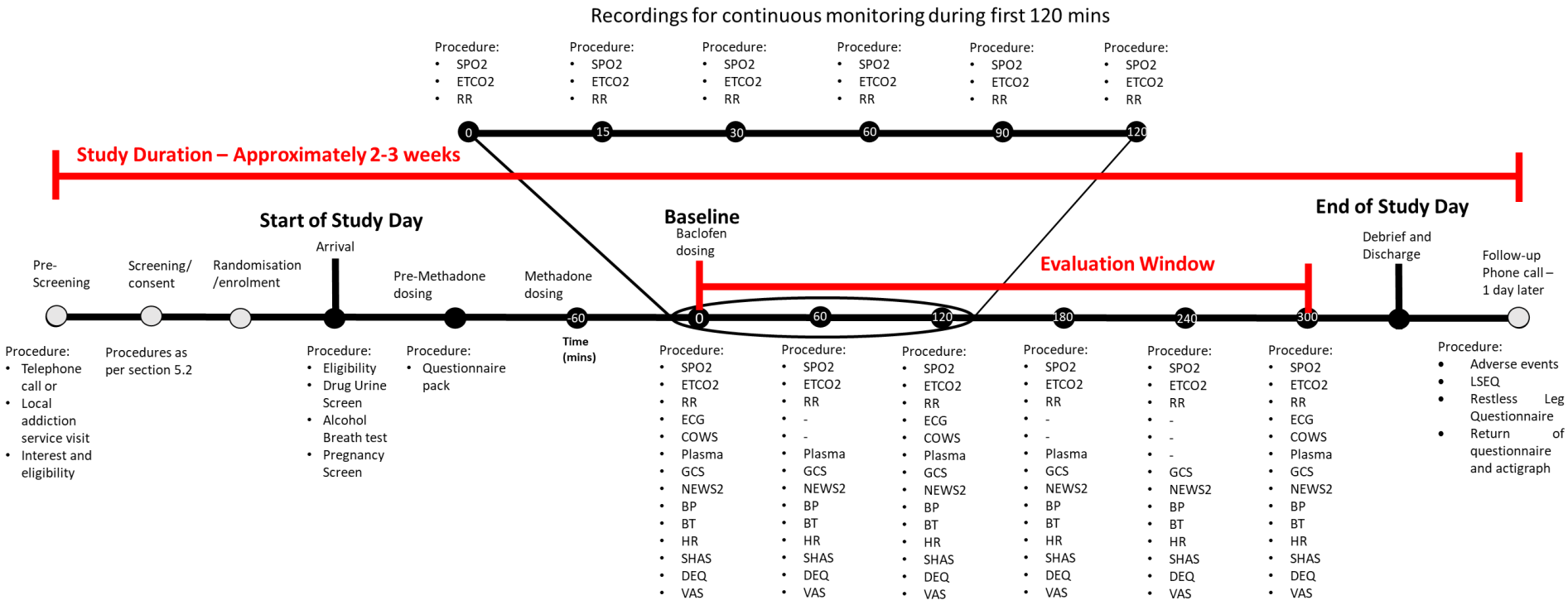
4.2 Study visits

All eligible participants will have:

- Pre-screening assessment by telephone or in their usual clinical addiction service, as appropriate
- One in-person clinical screening visit.
- Randomisation/enrolment
- One in-person experimental study visit
- One follow-up phone-call following the experimental study visit to check for adverse events.

4.3 Study design schematics

4.3.1 Study procedure schematic



Key: **SPO2**; Blood Oxygen Saturation, **ETCO2**; End Tidal Carbon Dioxide, **RR**; Respiration Rate, **ECG**; Electrocardiogram, **COWS**; Clinical Opiate Withdrawal Scale, **Plasma**; Blood Sample, **GCS**; Glasgow Coma Scale, **NEWS2**; National Early Warning Score 2, **BP**; Blood Pressure, **BT**; Body Temperature, **HR**; Heart Rate, **SHAS**; Subjective high assessment scale, **DEQ**; Drug Evaluation, Questionnaire, **VAS**; Visual Analogue Scale, **LSEQ**; Leeds Sleep Evaluation Questionnaire.

4.3.2 Experimental Visit Schematic

Experimental study day duration will be approximately 6-7 hours. Start times will be determined according to participant's preference but a typical study day would look like this:

Procedure	**Timepoint (mins)**								
	#Baseline	15	30	60	90	120	180	240	300
NEWS2	x	-	-	x	-	x	x	x	x
SpO_2	x	x*	x*	x	x*	x	x	x	x
RR	x	x*	x*	x	x*	x	x	x	x
BP	x	-	-	x	-	x	x	x	x
HR	x	-	-	x	-	x	x	x	x
Body Temp	x	-	-	x	-	x	x	x	x
LOC	x	-	-	x	-	x	x	x	x
GCS	x	-	-	x	-	x	x	x	x
ECG	x	-	-	-	-	x	-	-	x
CO_2	x	x	x	x	x	x	x	x	x
SHAS	x	-	-	x	-	x	x	x	x
DEQ	x	-	-	x	-	x	x	x	x
VAS	x	-	-	x	-	x	x	x	x
Blood Plasma	x	-	-	x	-	x	x	-	x
COWS	x	-	-	-	-	x	-	-	x

#Baseline refers to measurements obtained prior to Time 0, which represents the time at which baclofen/placebo is administered. Shaded area are measures comprising the NEWS2 score. *At these time points SpO_2 and RR measures will be taken in addition to those associated with the NEWS2.

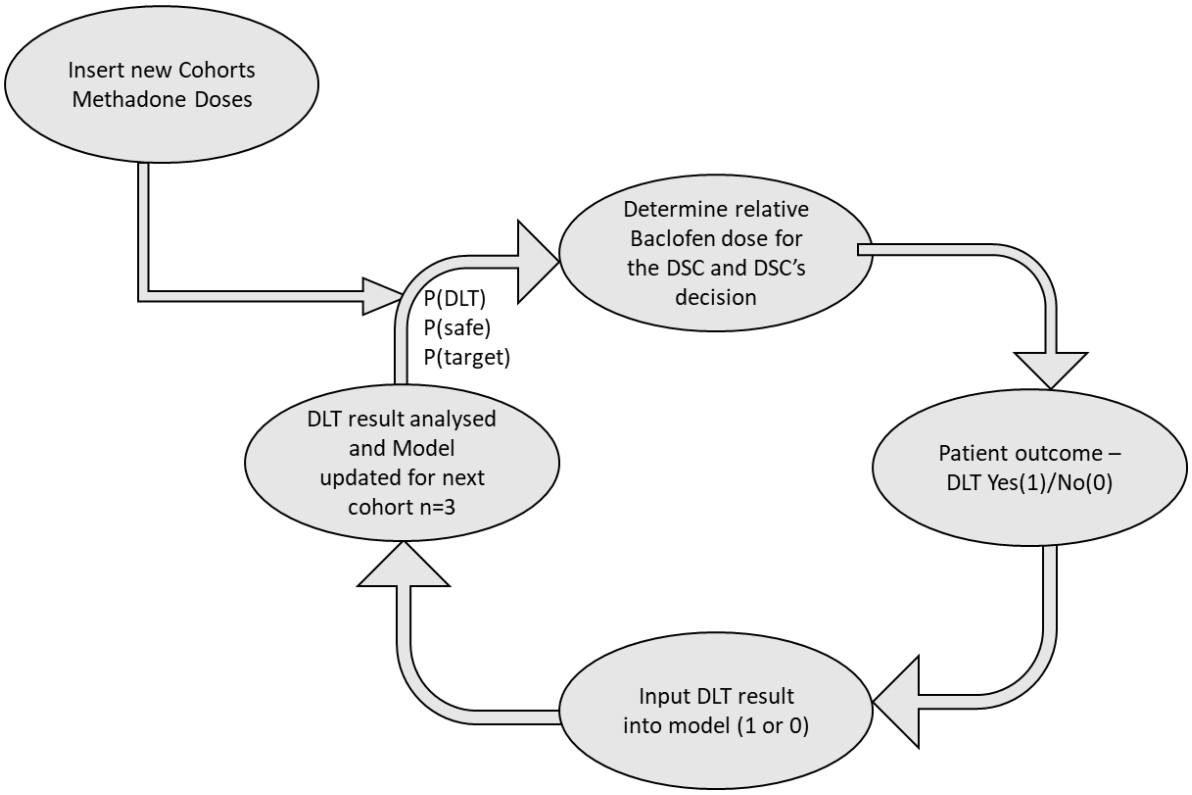
4.4 Treatment algorithm

A Bayesian dose-escalation adaptive model will be used to determine the baclofen dose allocation and will be informed by the occurrence of dose-limiting toxicity (DLT) events at increasing doses of baclofen (10, 30, 60, 90mg). Participants will be randomised (single-blind) to baclofen or placebo in a 3:1 ratio. If allocated to baclofen, the adaptive model will recommend the dose level for a given patient according to their prescribed dose of methadone and prior information regarding the incidence of DLTs. The model will be updated after each group of up to 3 participants, according to the observed patients' responses. The Dose setting committee (DSC) retains the ability to override the algorithms dose recommendation if clinically indicated.

The study can therefore be stopped earlier for safety if the model suggests that 30mg of baclofen and 60mg of methadone is highly likely to be *unsafe*. The study can also stop

earlier if the highest dose of baclofen (90mg) is highly likely to be *safe*, i.e. below the target toxicity with 120mg of methadone, provided that the study has also achieved sufficient data to meet secondary endpoints.

4.4.1 Schematic for baclofen dose algorithm



Please see section 4.4.2 for definitions of p(DLT), p(safe), p(target)

4.4.2 Baclofen dose decisions

The lowest dose of baclofen (10mg) will be allocated to the first group of 3 participants assigned to receive baclofen. The dose-toxicity model will be continuously updated after each group of at most 3 participants, to recommend dosing for the subsequent group of participants. The model will describe the probability of a patient experiencing a DLT; p(DLT), at a given methadone-baclofen dose, the probability of the given dose being safe; p(safe), and the probability of the dose being within the target toxicity interval; p(target).

The model will establish the combination-toxicity relationship which borrows information between different doses across both drugs, leading to an efficient use of data. The model will output the dosing function that provides the safe dose of baclofen that is most likely to be associated with 15-25% DLT risk for a given dose of methadone.

According to the model, if any of these DLTs are met, then the next group of patients will be assigned to the current (or lower) dose of baclofen, without dose escalation,

depending on the prescribed dose of methadone for the next individual that enters the study.

If there is no DLT, a dose escalation may be advised by the model, again, depending on the prescribed dose of methadone for the next individual that enters the study.

The model will recommend to stop the trial earlier due to safety concerns if the probability that the risk of DLT for 60mg of methadone in combination with 30mg of baclofen exceeds the target range is 25% or more. The model will recommend to stop the trial earlier due to all doses of baclofen being safe if the probability that the risk of DLT for 120mg of methadone in combination with 90mg of baclofen does not exceed the target range is 92.5% or more, representing the 'all-safe-stop criteria'.

The Dose Setting Committee (DSC, comprised of a statistician, clinician and member of the research team) can decide to over-ride any recommendation made by the model, if clinically indicated. Outside of the model parameters, clinical judgement will determine whether responses to baclofen are sufficiently concerning to cease escalation, escalate to a lower dose than planned by the model, or to reduce the average methadone dose for each dose of baclofen examined. If doses of 90mg baclofen are deemed safe by the model with up to and including 120mg methadone, further escalation will cease provided that the data required for secondary endpoints are met.

Should the study team witness multiple DLTs, using their clinical experience they can halt the trial early over safety concerns.

In the scenario that there is a very high probability that all doses are safe before reaching the maximum recruitment of n=48 receiving baclofen, the study will retain the ability to override the all-safe-stop criteria to continue recruitment until we have tested a sufficient range of doses of methadone to ensure we have covered the clinical range of potential methadone doses and/or to explore baclofen dose separation to achieve maximum precision on secondary outcomes.

Given no safety concerns, we expect the *minimum* numbers of participants at each of the doses to be as follows: n=3 @10mg baclofen, n=3 @ 30mg baclofen, n=12 @ 60mg baclofen and n=12 @ 90mg baclofen, with n=10 receiving placebo, providing sufficient data to allow adequate exploration of dose separation on primary and secondary outcomes across a range of methadone dose levels, and an assessment of GABA-B receptor sensitivity and any gender effects. These numbers might be exceeded if the variability in response is larger than anticipated, female representation is lower than we would like, or we have not yet been able to test the full range of methadone doses. If a particular baclofen dose is deemed unsafe, then the lower doses would be similarly explored.

5 STUDY PROCEDURES

5.1 Pre-Screening Procedures

Pre-screening appointments will take place via telephone or within the local addiction services as appropriate, to ensure that participants are likely to be interested, and eligible according to DSM-5 and study criteria. This will take approximately 20 minutes.

5.2 Screening Procedures

Informed consent will take place either at the Imperial Clinical Research Facility, or at the local addiction service within CNWL, or other HRA approved specified sites, as required. The local addiction service where participants are receiving treatment, and/or the participants' general practitioner will be notified of their patient's participation.

5.2.1 Consent

The PIS and consent forms will be read through carefully with the participant. If they wish to participate, they will be informed that participation is entirely voluntary and that they can leave the study at any time without their decision affecting the treatment that they will be receiving. Written informed consent will be taken by a member of the research or clinical team under the supervision of the chief investigator.

Consenting participants will undergo enrolment and routine screening to ensure they are medically fit and eligible to take part. Members of the research team will discuss the study in detail, and the subject's eligibility to participate assessed against inclusion and exclusion criteria. A clinical member of the team will take a detailed clinical history of current and previous health and perform a physical examination to check for current health. In addition to eligibility assessment through history and examination, blood tests will be undertaken, where it is deemed clinically necessary e.g. if participant has a history of kidney/hepatic impairment that requires confirmation of current status.

Screening visits will last approximately 2-3 hours. For the majority of participants, the screening procedures will take place at the Imperial Clinical Research Facility (CRF) at Hammersmith hospital. However, to provide flexibility for our opiate dependent participants, the screening visit may be undertaken within our partner trust at Central and North West London NHS Foundation (CNWL) trust (CIPPres clinic), or certain aspects of screening (e.g. consent, questionnaires) may be completed at the local addiction service within CNWL, as applicable, to reduce the cognitive burden and increase study flexibility, acceptability and compliance.

Participants will undergo the following procedures at the screening visit:

5.2.1 Pregnancy test

Female participants will undertake a urine pregnancy test.

5.2.2 Breath Alcohol Level

Screening for alcohol content will be conducted with alcohol breath test. Additional random alcohol screens may be performed during the study at the Investigator's discretion.

5.2.3 Urine Drug Screen

Urine will be screened for drugs of abuse including amphetamines, benzodiazepines, cannabinoids, cocaine, methadone, opiates. Participants will be assured that results of these tests (and all other information obtained in the study) are confidential and will not be reported to key workers, GP or participating addiction services.

5.2.4 Vital statistics and Vital signs

Height, weight and body mass index will be measured. Vital signs will comprise systolic and diastolic blood pressure, pulse rate, body temperature and blood oxygenation.

5.2.5 Medical examination

Medical examination will be assessed by structured interview as related to the eligibility criteria listed.

5.2.6 Physical Examination

Physical examination will include assessments of the head, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen, lymph nodes and extremities.

5.2.7 Respiratory Examination

Participants will be asked about risk factors for respiratory disease e.g. history of persistent cough or breathlessness at rest, previous verified diagnosis of chronic obstructive pulmonary disease (COPD), hospital admission due to COPD, non-invasive ventilation for type 2 respiratory failure, use of inhalers for respiratory compromise, ventilation due to COVID-19, history of inhalation/smoking of substances e.g. heroin, tobacco, crack cocaine.

If further tests are clinically indicated to determine signs of current COPD or respiratory function, participants will undergo a 6 minute walk test with SpO_2 monitoring, for signs of respiratory compromise.

If clinically indicated, participants will complete spirometry examination to measure forced expiratory volume/forced vital capacity (FEV1/FVC) ratio. Due to COVID-19 restrictions for aerosol generating procedures (AGPs), this may be undertaken outside or at home under guidance of the study team via video link.

5.2.8 Blood samples for clinical laboratory testing

Given that blood sampling is required for the experimental visit, an assessment of venous access will be made. Blood samples will be collected via venepuncture if clinically indicated e.g. for full blood count, urea and electrolytes, and liver function tests. Venous access is a particular problem that is common in injecting heroin users, therefore failure to provide a blood sample will not exclude a participant as long as all other eligibility criteria are met and clinicians are satisfied that participation will be safe.

5.2.9 Psychiatric history, drug & alcohol history, demographics

Psychiatric diagnoses according to DSM-5 criteria will be assessed by a psychiatrist, or by a study clinician and reviewed by a psychiatrist. Semi-structured interviews for assessment of sleep, alcohol, nicotine and drug use will be conducted, including a record of abstinence periods, recent on-top use. Demographic parameters will be captured in the case report form.

5.2.10 Questionnaire measures

The following validated questionnaires will be administered to aid diagnoses and for characterising clinical status:

Mini International Neuropsychiatric interview (M.I.N.I.) (Sheehan DV et al., 1998)
Beck Depression Inventory, BDI-II, (Beck et al., 1996)
STAI; Spielberger State & Trait Anxiety Scale, (Spielberger et al., 1983)
Visual Analogue Scales (VAS) of craving, anxiety
Severity of Dependence Scale; SDS, (Gossop et al., 1995)
Obsessive-Compulsive Drug Use Scale; OCDUS-H, (Franken et al., 2002).
Fagerstrom test for nicotine dependence (Heatherton et al., 1991)
Alcohol, Smoking, Substance Involvement & Screening Test (ASSIST)
Alcohol current intake (AUDIT)
Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989)
Epworth Sleepiness Scale (ESS) (Johns, 1991)
Restless legs severity scale (RLS scale), https://www.rls-uk.org/diagnosis

5.2.11 Cardiovascular measures

An ECG will be obtained at screening to determine suitability for QT measurements. If the initial QTc value is prolonged, the ECG should be repeated two more times (with 5 minutes between ECG readings) and the average of the 3 QTc values used to determine eligibility.

5.2.12 Actigraphy measures

An actigraph to remotely monitor sleep-wake cycles will be administered to eligible participants to wear continuously until the day after the experimental visit. This is a non-invasive wrist-worn device that captures movement.

5.3 Enrolment procedures

Participants who are eligible at screening will be invited to attend the experimental study visit and upon confirmation of attendance will undergo enrolment and randomisation.

5.3.1 Anonymisation and randomisation

Each participant will be given a unique participant identification number upon entering the study which will not change.

The randomisation to either baclofen or placebo (3:1 ratio) will be performed using the online software application, Sealed Envelope TM.

Then the participant's current prescribed dose of methadone will be entered into the Bayesian adaptive model which, in conjunction with previous DLT toxicity data, will

recommend the baclofen dose to be assigned as either 10, 30, 60 or 90mg baclofen. As previously stated, this recommendation can be over-ridden based on cumulative clinical experience. The adaptive Bayesian model will be programmed into R. A custom-built OpenClinica Clinical Data Management and Electronic Data Capture software database, will store the output of the randomisation and baclofen dose where relevant.

After randomisation, if a participant does not attend the experimental visit within the expected time window, the research team will have the option to replace this individual with a new participant, as appropriate. The new participant would receive the same allocation of placebo or baclofen, but if allocated to baclofen the allocated dose might change, depending on the methadone dose-level and recommendation of the adaptive model at that point in time. This would not exclude the replaced participant from re-entering the study at a later date, at which point they would be re-randomised.

After randomisation, all paper and electronic case report forms will utilise the participant study ID number, rather than personal identifiers wherever possible.

5.4 Experimental study visit procedures

Experimental study visits will take place at the NIHR Imperial Clinical Research Facility (CRF) at Hammersmith hospital, lasting approximately 6-7 hours (with breaks). This follows previous protocols which have been acceptable and well tolerated by participants. At each study visit participants will take their usual dose of methadone, undergo baseline assessments and receive a single dose of orally administered placebo or baclofen. Measures of safety, PK-PD, self-report questionnaires and adverse effects will be taken prior to, and at regular intervals following baclofen administration, according to section 4.3, to coincide with peak plasma concentrations, peak anticipated pharmacodynamic response and for up to 5 hours, allowing adequate rest breaks for participants.

The following assessments will take place:

5.4.1 Eligibility check

Participants will arrive at the research centre and confirm consent. Transport will be arranged where appropriate. Refreshments made available throughout the day. Lunch will be provided. Smoking is permitted at regular intervals as required, to avoid nicotine withdrawal, but smoking will be avoided in the 15 minutes prior to each hourly time-point and during the first 2 hours following dosing. Caffeine intake will be permitted (according to usual consumption).

Upon arrival, eligibility will be checked and drug urine screen, alcohol breath and pregnancy tests obtained (see procedures above)

5.4.2 Methadone Dosing

Participants will take their usual dose of prescribed daily methadone, and the time noted.

NB: In those receiving daily prescription methadone, given their long-term use, plasma levels will be at steady-state during the day. The vast majority of participants take their methadone in the morning, therefore on experimental visits, participants will bring their

usual methadone dose with them to the research facility, and consume it under observation on the premises, shortly after arrival. Maximal plasma levels of methadone are reached in 1.8-3.8h with half-life of ~24hrs (independent of dose, (Wolff et al., 1993). Our previous experience is that a short delay in taking methadone is acceptable to participants and we do not anticipate substantial discomfort. However, to minimise this, the methadone will be taken as early as possible, and the gap between methadone and baclofen administration will be kept short (~40-60 minutes).

5.4.3 Baclofen or Placebo Dosing & Administration

The dose recommendation from the model will be administered approximately 1 hour after methadone. The dose levels are 10mg, 30mg, 60mg or 90mg, administered as either 1, 3, 6 or 9 tablets of baclofen respectively, or a matching number of placebo (vitamin D) tablets which are a very close visual match (see section 5.7).

Effects of baclofen or placebo will be monitored for up to 5 hours following dosing at the Clinical Research Facility. Any lasting effects will be monitored at a follow-up telephone call the following day.

Placebo or baclofen tablets will be administered with water by a nurse or study team member under direct supervision. Participants will not be given the chance to scrutinise the contents of the medication pot prior to consumption. This is a single-blind trial, therefore the participants will not be aware of whether they are taking placebo or baclofen tablets.

NB Baclofen reaches peak maximum concentrations approximately 1-2 hours after oral dosing with 60mg (C_{max}; 88-102 minutes, (Durant et al., 2018), and has an estimated half-life in plasma of ~3 hours after a single 60mg dose (range = 2.7-3h from 10-90mg baclofen). All testing will therefore be covered by baclofen's pharmacokinetic profile.

5.4.4 Respiratory measures

Following baclofen administration, continuous monitoring of the patient will occur for the first 120 minutes.

Blood gases: Pulse oximetry, capable of continuous recording, will be used for regular static, and periodic continuous monitoring and recording of the blood oxygen saturation whilst seated, or semi-supine.

For safety, whilst the participant is not under direct supervision but remaining in the ICRF, continuous pulse oximetry will continue to be monitored at the remote nursing station for the first 120 min following drug administration.

Capnography and/or transcutaneous CO_2 measurements will be obtained at regular intervals, with periodic continuous monitoring and recording of $ETCO_2$/partial pressure and respiratory rate via a nasal cannula.

5.4.5 Intervention measures

Intervention levels (0 to 4) will be utilised if marked sedation occurs (see section 3.4.3).

5.4.6 Sedation measures

Glasgow Coma Scale (GCS) will be obtained at baseline (after methadone dosing), and then every hour following baclofen dosing. The GCS assesses the participant's ability to open their eyes, move and speak, and has a minimum score of 3 with a maximum of 15.

National Early Warning Score 2 (NEWS2) for clinical deterioration. It is a staff rated aggregate scoring system (not self-report), with the magnitude of the score reflecting how extremely the parameter varies from the norm. The minimum score of zero and maximum of 20 and comprises the following 6 physiological parameters:

1. Respiratory rate
2. Oxygen saturation
3. Temperature
4. Systolic blood pressure
5. Pulse rate
6. Level of consciousness or new confusion (ACVPU; alert, confusion, voice, pain, unresponsive) score

5.4.7 ECG measures

An ECG to measure possible QT prolongation will be obtained at 3 timepoints; baseline (after methadone dosing), after anticipated peak effects (t=120min) and prior to discharge (approx. 5-6h post-dose). If the initial QTc value is prolonged, the ECG should be repeated two more times (with 5 minutes between ECG readings) and the average of the 3 QTc values taken.

5.4.8 Vital Signs

Under direct observation, heart rate will be measured at regular static time points whilst seated, or semi-supine. For safety, whilst the participant is not under direct supervision but remaining in the ICRF, continuous pulse oximetry will monitor heart rate at the remote nursing station.

Blood pressure will be measured via a cuff at before and after methadone dosing, and at regular static time points whilst seated, or semi-supine, every hour following drug administration dosing.

Body Temperature will be monitored as part of the MEWS score, using an aural thermometer.

5.4.9 Visual analogue scales

Visual analogue scales (VAS) will be used to assess mood and drug effects including drug liking, anxiety and craving which will be assessed before and after baclofen administration at regular time points throughout the study day – these will allow us to document the known central effects of baclofen if any.

5.4.8.1 Drug effects (general) scales

Subjective High Assessment Scale (SHAS) will be obtained at baseline, before and after methadone dosing, and every hour following baclofen dosing.

5.4.8.2 Drug effects & Liking scale

Drug Effects Questionnaire (DEQ; feel, liking, dislike, high, want more)

5.4.8.3 Other

VAS for craving, anxiety

5.4.10 Other questionnaires

The Clinical Opiate Withdrawal Scale (COWS, (Wesson & Ling, 2003)) will be administered at baseline, and again at 2 further time-points to check that the participant is not in overt withdrawal.

5.4.11 Plasma levels – Baclofen, Methadone, Growth Hormone

Plasma concentrations of baclofen, methadone and growth hormone will be measured from whole blood. Blood samples of up to 10ml will be obtained at baseline and 1, 2, 3, 5 hours after dosing, in total a maximum of 50ml blood.

5.4.12 Adverse events

Emergence of side effects of baclofen will be assessed as appropriate and recorded according to the MedDra dictionary.

5.4.13 Actigraphy

The wrist worn-actigraphs administered at the screening visit will be checked and re-administered for return the following day.

5.4.14 Debrief

Participants will be asked about their experience of the session; whether they could guess whether they had placebo or drug, whether they thought it was a low or a high dose, and whether at any time they liked the drug effects they encountered.

5.4.15 Discharge

Participants will be required to remain under supervision for a period of 5 hours after they receive baclofen/placebo, and remain at the research facility until approved for discharge by the study physician. Staff will ensure that any adverse impacts etc have attenuated before the participant leaves. Study staff will remind participants of relevant study contact details, including a 24-hour mobile telephone number for the on-call study doctor.

Where possible, study staff will arrange for a taxi to take the participant home.

5.4.16 Emergency contact

Provided by on-call study doctor via study mobile.

5.5 Follow-up

Following completion of experimental study visits, participants will be telephoned the day after the visit to check for the following:

- adverse events

- complete sleep and restless legs questionnaire- Leeds Sleep Evaluation Questionnaire (LSEQ, (Parrott AC and Hindmarch I. 1980)
- arrange return of questionnaires and actigraph
- If the participant is still sedated during the call, a second follow up will occur later that day or the following day.

The questionnaires can be completed online, or returned along with the actiwatch in a stamped addressed envelope or via the clinical service.

Any incidental findings will be discussed with the individual and appropriate action taken which could include passing information to GP and/or clinical addiction team as required**.**

5.6 Schedule of events

Event	Screening	Enrolment	Experimental	Follow-up
GENERAL				
Consent & eligibility	x		x	
General health	x		x	x
Demographics	x			
CLINICAL ASSESSMENTS				
Structured clinical interview (MINI)	x			
Medical examination	x			
Vital statistics (height, weight)	x			
Vital signs (BP, HR, SpO_2)	x		x	
Respiratory function	x		x	
Blood sampling (clinical)	(x)			
Urine screen (DOA & pregnancy)	x		x	
Breath alcohol	x		x	
Methadone administration			x	
Baclofen administration			x	
DRUG & ALCOHOL HISTORY				
MTD dose check	x		x	
TLFB (drug & alcohol use)	x			
FTND	x			
AUDIT	x			
ASSIST (shortened)	x			
SDS	x			
OCDUS-H	x			
RANDOMISATION				
Randomisation & Enrolment		x		
MOOD & PERSONALITY				
BDI	x			
STAI	x			
SSAI	x			
BIS	x			
UPPS-P	x			
PSQI	x			
ESS	x			
STATE MEASURES				
VAS drug effects (DEQ)			x	
VAS craving	x		x	
VAS anxiety			x	
COWS	x		x	
LSEQ, sleep quality			x	x
Adverse events			x	x
BLOOD MEASURES				
Growth hormone			x	
Baclofen/Methadone			x	
ACTIGRAPHY MEASURES				
Actigraphy	x	x	x	x

5.6.1 Protocol events flexibility

Whilst we will endeavour to complete all the questionnaires and tasks as detailed in the protocol if at the experimental visits it seems that the burden is too great on the participants, we will minimise this by omitting any unnecessary questions, questionnaires or tasks from the protocol, whilst still maintaining sufficient data to meet criteria for an evaluable participant, following discussion within the team as to the best course of action.

5.7 Study medications

Baclofen (generic) tablets are expected to be acceptable to participants and well tolerated. The placebo will be Vitamin D_3 (generic) tablets which are not expected to result in any noticeable effects or mood changes and are expected to be very well tolerated. Vitamin D tablets provide a good visual match to the baclofen tablets. Participants will not be told that the placebo tablets contain vitamin D as this could also create expectation effects. Instead they will be told that these are 'dummy' pills, and we will check for vitamin D contraindications at screening.

Participants will be randomised to receive oral baclofen (acute dose of 10, 30, 60 or 90mg), or placebo (an equivalent number of Vitamin D tablets), in a 3:1 ratio in a single-blind design.

The dose will be recommended by the adaptive model algorithm. We will administer baclofen 10mg as 1 x 10mg tablets, 30mg as 3 x 10mg tablets, 60mg as 6 x 10mg tablets and 90mg as 9 x 10mg tablets. The placebo group will receive the same number of Vitamin D tablets, according to the model recommendation, up to a maximum of 6 tablets, assuming the dose per tablet is 20 micrograms (total dose 120 micrograms or 4800IU).

Example SmPC for Vitamin D (Desunin, colecalciferol 20 micrograms/800IU)
https://www.medicines.org.uk/emc/medicine/27007#gref

5.7.1 Baclofen in licensed indication

For baclofen, BNF recommended maximum dose is 100mg/d for licensed indication of spasticity. Example SmPCs for generic baclofen can be found here:

Accord UK Ltd (10mg tablets)
https://www.medicines.org.uk/emc/product/5728/smpc
Advanz Pharma (10mg tablets)
https://www.medicines.org.uk/emc/product/11781/smpc
Mylan (10mg tablets)
https://www.medicines.org.uk/emc/product/2594/smpc

Baclofen is the only selective GABA-B agonist licensed for human use. Originally developed as a potential anti-epileptic in the 1920s, it was found to have anti-spastic effects and is currently used for the treatment of spastic movement, especially in instances of spinal cord injury, spastic diplegia, multiple sclerosis, and amyotrophic lateral sclerosis. It is an orally active g-aminobutyric acid (GABA) derivative, p-

chlorophenyl-gamma aminobutyric acid. Its primary action as an antispasticity agent is via simulation of $GABA_B$-receptors resulting in depression of monosynaptic and polysynaptic reflex transmission. Baclofen increases K^+ conductance resulting in postsynaptic inhibition and reduces Ca^{2+} influx and the release probability of excitatory transmitters (glutamate and aspartate) causing presynaptic inhibition in the brain and spinal cord (Katzung, 2009). Baclofen also exerts an antinociceptive effect and may act at supraspinal sites producing CNS depression. Baclofen may also modulate dopamine release in the mesocorticolimbic system by targeting neurons in the ventral tegmental area (Cruz et al., 2004).

Over its many years of use, baclofen has proven to be a very safe drug with few side effects. The main adverse effects of are somnolence, dizziness, muscle weakness, and headache. Baclofen has good absorption after oral administration (75%), with peak serum concentrations achieved in 2–4 h. It is weakly bound (30%) to plasma proteins, and is eliminated primarily via the kidneys, 85% as the unchanged parent compound, with an estimated elimination half-life of 3-4 hours. The therapeutic serum concentration for spasticity is 0.08 to 0.4 microgram/ml.

5.7.2 Additional Supporting Information for the dose of baclofen

5.7.2.1 Baclofen in Alcohol dependence

Very high doses of baclofen have been reported for use in alcohol use disorder for some patients (≤300mg/d), which is 10 times higher than that used in the initial RCT in this indication. Meta-analyses established an efficacy signal in alcoholism with ≤60mg/d compared with higher doses. Baclofen doses below 30mg/d have not demonstrated efficacy in alcoholism. A temporary license was granted in France for this indication up to 80mg/d (see section 2). In addition, we have comparative data using acute doses up to 90mg in our healthy control and alcoholic cohort showing that doses up to and including 60mg in controls and up to 90mg in alcohol dependent individuals were well tolerated (Durant et al., 2018). NB Only 10mg doses are available in the UK, making planned dose escalations of 10, 30, 60 and 90mg those most practicable options.

We reviewed the trials of baclofen in alcoholism to determine how they evaluated side-effects and adverse events, as there is no universally accepted gold-standard assessment (Singh & Loke, 2012). A systematic review of trials of baclofen in alcoholism (Pierce et al., 2018) reported that 9 of the 13 published studies reported no serious adverse events with one study not describing any such data. Of the remaining, the study with the highest prevalence of adverse effects investigated the highest dose of baclofen (Reynaud et al., 2017); <180mg/d)). It reported that 20 baclofen and 26 placebo patients experienced 40 and 43 serious adverse events (e.g. hospitalisation for alcohol detoxification, fall, suicidal ideation, depression) but most (70%) were considered unrelated to study medication. The other 2 studies reported one medication related serious adverse event: hospitalization due to constipation (Beraha et al., 2016); <150mg/d) and one overdose (related to medication), two hospitalisations due to suicidal ideation/intoxication (possibly medication related), and one death (30mg/d, provisionally assessed as unrelated to medication; (Morley et al., 2018)). In all the trials, common side effects reported included sleepiness/drowsiness, vertigo, fatigue, dry mouth, headache, sleep disorders, asthenia/muscle weakness, and dizziness and which were more likely to be observed following higher (ie >100mg/d) doses than will be used in our study (Pierce et al., 2018; Rose & Jones, 2018). In summary, whilst many

patients taking baclofen will incur side-effects these are generally benign and attenuate within first few days (or with slower titration/dose reductions); potentially more serious ones include seizures, respiratory depression with sleep apnoea, severe mood disorders, and mental confusion/delirium and potentially coma, particularly in case of intoxication with alcohol or other sedative drugs or after taking a baclofen overdose (de Beaurepaire et al., 2019).

We have been unable to find any reports that baclofen is hepatotoxic and baclofen has been proposed as ideal in alcoholism where liver impairment is common. The first RCT of baclofen in alcoholism was in patients with cirrhosis where liver function improved (G. Addolorato et al., 2007). A study in patients with Hepatitis C reported that baclofen was well tolerated and there were no differences between groups in rates of serious drug-related adverse effects and discontinuation (Hauser et al., 2017). Thus studies and reports from clinical populations suggest that baclofen is well tolerated in patients with chronic liver disease (de Beaurepaire et al., 2019). It is recommended that baclofen not be used in patients with hepatic encephalopathy or hepatorenal syndrome but these are extremely unlikely in those undergoing community opiate detoxification as they would not be healthy enough (Leggio & Lee, 2017; Thursz et al., 2018)

5.7.2.2 Baclofen dose in opiate dependence

Our previously conducted pharmacokinetic-pharmacodynamic (PK/PD) study to investigate the sensitivity of the GABA-B system demonstrated that alcohol dependent participants were less sensitive to the subjective and objective effects of baclofen than healthy controls (Durant et al 2018), and evidence from elsewhere suggests the same might be true for opiate dependence (Volpi et al., 1992).

Details of all previous studies (to our knowledge) investigating baclofen in opiate dependence are provided in Table 1 and section 2.4. Doses of baclofen ranged from 40 to 80mg/day. No safety issues were reported, and baclofen was described as well tolerated with few adverse events.

More specifically, Krystal et al (1992) reported that 80 mg/day of baclofen was tolerated without evidence of side effects in patients whose methadone was abruptly stopped. In the Iranian studies of opiate detox, data was not presented regarding side-effects in one (Akhondzadeh et al., 2000). The other reported no overall difference in side-effect profile with baclofen compared with clonidine however, headache, nausea and vomiting were seen more with baclofen and dry mouth and orthostatic hypotension more with clonidine (Ahmadi-Abhari et al., 2001). No difference was reported in side-effects or adverse events between baclofen and placebo during a trial for relapse prevention in opiate dependence (Assadi et al., 2003).

5.7.3 Pharmacy and packaging

Drugs will be stored at Hammersmith hospital (HH) pharmacy and dispensed according to the prescription, which will be completed by the study physician. Dispensing and management of drug accountability will be managed and conducted by HH Pharmacy according to their SOPs. Prescriptions & Drug accountability logs will be maintained by the research team.

5.7.3.1 Baclofen

Baclofen (generic) will be supplied by Imperial College Healthcare NHS Trust pharmacy (Hammersmith Hospital). These are white, round, scored tablets. Labelling will be as per Annex 13 regulations and dispensed under Regulation 37 of the 2004 UK Clinical Trial Regulations within the hospital, according to the exemption contained therein.

5.7.3.2 Placebo

Placebo tablets will be vitamin D_3, (colecalciferol; scored, white round tablets) that are a near identical match to baclofen, supplied by Imperial College Healthcare NHS Trust pharmacy (Hammersmith Hospital). Labelling will be as per Annex 13 regulations and dispensed under Regulation 37 of the 2004 UK Clinical Trial Regulations within the hospital, according to the exemption contained therein.

5.7.4 Emergency Unblinding Procedure

This is single-blind- study clinicians and researchers will be aware of the drug allocation that was recommended by the adaptive trial algorithm and this allocation will be stored within the OpenClinica Database and accessible to the research team.

5.8 Study Durations

5.8.1 Protocol in event of experimental day failure

In the event that a participant does not attend as planned, or tests positive for alcohol or drugs of abuse, or is ineligible for the study day (e.g. positive covid test, illness) prior to baclofen administration, the experimental visit will be re-scheduled. The participant would retain their baclofen or placebo randomisation, and their baclofen dose allocation. However, depending on the length of time between the cancelled and re-scheduled visit, and the potential for updates to the adaptive model in the intervening time, the baclofen dose level may be re-allocated, according to the discretion of the Dose Setting Committee.

In the event that a participant has been administered medication during an experimental study visit, and there is subsequently a problem (e.g. fire alarm, non-recoverable equipment malfunction), that results in significant data loss such that the participant does not meet criteria for an evaluable participant, with the continued consent of the patient the study day (including drug administration) will be repeated at another scheduled session (in at least 5 days' time if participant was randomised to baclofen).

In the event that a participant does not re-schedule and is considered 'lost', that participant can be replaced if required (i.e. to make total of 48 on baclofen if safety has not yet been established). The replacement participant should receive the same treatment (placebo or baclofen) of the participant that is being replaced. However, in this case, the baclofen dose level may be re-allocated, as informed by the current model based on the replacement person's own methadone dose, and at the discretion of the Dose Setting Committee.

5.8.2 Withdrawal of Participants from the Study

Participants can initiate withdrawal from the study. Each patient that will be recruited has the right to withdraw from the study for any reason. All data and samples collected to date will be retained. Should a participant decide to withdraw from the trial, all efforts

will be made to report the reason for withdrawal as thoroughly as possible and they will be encouraged to continue to provide outcome data.

5.8.3 Duration of the study period

The duration of the study period will be approximately 2-3 weeks for participants to complete consent, screening, experimental study visit and follow-up. In the event of a longer delay between screening and experimental visit, certain screening activities may be repeated at the discretion of the clinical team.

5.8.4 Flexible visits

We wish to minimise the drop-out rates and make participation as easy and flexible for participants as possible (particularly opiate dependent). Therefore participants may decide to undertake certain screening assessments over several visits, e.g. they may wish to participate by phone, online video or via an in-person visit in their local addiction service rather than at the ICRF. Subject to the relevant HRA approvals being in place, flexible visits for this purpose will be permitted.

5.8.5 Duration of the follow-up period

The duration of the follow up period will be 1 day for all participants who will receive a phone call the day after the experimental study visit.

5.8.6 Loss to follow-up

It is anticipated that more subjects will complete initial screening assessment than the experimental visit. Unless participants actively withdraw participation, data will be retained and analysed, as appropriate.

5.8.7 Definition of completion of the study for an individual participant

The end of the study will be defined as the last telephone contact visit which is 1 day after their study visit for opiate dependent participants. This represents the end of data collection as defined in ethics and regulatory terms, after which, adverse events will not be recorded.

5.8.8 Definition of the end of the study

The completion of the study for regulatory purposes will be defined as the last telephone follow-up appointment for the last participant.

6 PARTICIPANT RECRUITMENT

6.1 Population

Opiate dependent participants enrolled in this study will be engaged in treatment for their opiate dependence from a specialist community addiction service and receiving stable doses of opiate substitution therapy with methadone. Therefore the participants will be regularly attending an addiction service, receiving psychosocial support. Therefore participants will not be chaotic with regard to their drug/alcohol use, unreliable in their attendance at appointments or have substantial physical or mental health needs.

In particular, the research team will endeavour to recruit participants from across the methadone-maintenance dose range, including both males and females, to maintain a

balanced design and to capture data that allows a representative assessment of safety across the clinical population.

6.2 Number of Participants

The sample size is not fixed. Up to a total of 64 patients are planned to be enrolled in the study with up to 48 patients on the experimental doses and up to 16 on placebo, as recommended by the trial algorithm in consultation with clinicians and the study team.

The drop-out rate from the study is estimated to be approximately 20% following screening. We therefore anticipate screening up to 100 methadone-maintained opioid dependent participants for entry into the study, with ~75% eligibility rate at screening, and a further ~20% drop out prior to, or at the experimental session.

6.2.1 Definition of successful completion

Successful completion will be defined as those meeting criteria for an 'evaluable patient' as defined in section 3.4.7. In the event of incomplete data, we will make a decision as to whether an individual's data will be included in the primary and secondary analyses on a case-by case basis.

For primary analysis, we will endeavour to include all those who received baclofen, if data allows a determination of whether or not a DLT was deemed to have occurred, according to clinical judgement.

For secondary outcomes, analyses will include those that have at least one measurement following drug administration.

6.3 Recruitment Strategies

Opiate dependent individuals will primarily be recruited from NHS substance misuse services and/or related voluntary sector services based in London and surrounding areas, by directed advertisement at those services, via referral, or via an investigator-led approach at NHS trusts, voluntary sector or partner organisations via Participant Identification Centres (PIC) or equivalent, subsequent to relevant approvals. Increasing visibility of the study and additional recruitment channels may also involve widespread advertisement in social media, dedicated study facebook pages or social media presence, and advertising on relevant websites related to addiction.

All advertising webpages will contain a link to a dedicated FORWARDS study website and/or email address which will provide a basic resource for further information, and study contacts such that the study team can contact participants as appropriate.

6.4 Eligibility Criteria

6.4.1 Inclusion Criteria

1. Male or female
2. Aged over 21
3. Willing and able to comply with protocol

4. Able to read, comprehend and record information written in English
5. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
6. Healthy as determined by a responsible physician, based on a medical evaluation which includes medical history, a physical examination, laboratory tests (if required), and a psychiatric evaluation. A volunteer with clinical parameters outside the reference range for the population being studied may be included, only if the investigators concur that the finding is unlikely to jeopardize either subject safety or study integrity.
7. DSM-5 diagnosis of current severe opioid use disorder
8. Treated with methadone substitution therapy and able to maintain the same stable dose for screening and experimental visit.
9. Ability to receive an acute dose of up to 90mg baclofen or up to 4800IU vitamin D (placebo).

6.4.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Intoxication on any of the visits, as assessed by difficulty in walking, the slurring of speech, difficulty concentrating or drowsiness. This exclusion criteria would exclude a subject from that study day only and not the whole study, at the discretion of the research team.

2. Positive urine drug screens or breath alcohol at screening or experimental testing visits. A minimum list of drugs that will be screened for include amphetamines, cocaine, opiates, methadone, cannabinoids and benzodiazepines. Positive results for methadone will be allowed for those opiate dependent participants still undergoing OST. Positive results for cannabinoids will be allowed given the long half-life of cannabinoid metabolites. This exclusion criteria would exclude a subject from that study day only and not the whole study, at the discretion of the research team.

3. Current DSM-5 substance dependence disorder for any other substance except for opiates and nicotine. Lifetime history of dependence on other substances will be allowed given very high incidence of co-dependence.

4. Regular on-top use of heroin or other opiates or other illicit substances in combination with OST, which in the opinion of the investigators will interfere with subject safety or study integrity.

5. Any participant taking over 120mg/day of prescribed methadone.

6. Current severe DSM-5 mental health disorder (excluding opiate dependence). Current moderate or mild DSM-5 depressive, anxiety, sleep or personality disorders will be allowed given the high levels of comorbidity, provided in the opinion of the investigators, the participant is able to complete study procedures satisfactorily.

7. Current or past history of enduring severe mental illness e.g. psychotic disorder (excluding drug induced), schizophrenia, bipolar affective disorder).

8. Active suicidality.

9. Use of regular prescription medications which in the opinion of the investigators will interfere with subject safety or study integrity. Regular use of psychotropic medication will be permitted e.g. antidepressants, provided the participant is compliant with administration and the investigators concur that they will not interfere with subject safety or study integrity.

10. Participants are taking any medication that is contraindicated with baclofen or placebo (vitamin D_3), or are hypersensitive to them or any of their excipients.

11. Participants that are taking any medication that in the opinion of the investigators may impact on the outcome measures during the experimental session.

12. Use of intermittent psychotropic medication which in the opinion of the investigators will interfere with subject safety or study integrity.

13. End stage or acute renal failure.

14. Severe chronic obstructive pulmonary disease (COPD) or Type 2 respiratory failure.

15. Pulse rate <40 or >100 BPM OR systolic blood pressure >160 and <100 and a diastolic blood pressure >95 and <60 in the semi-supine position.

16. Oxygen saturation <92% at rest

17. A screening ECG with a QTcB or QTcF > 500 msec or an ECG that is not suitable for QT measurements (e.g. poorly defined termination of the T-wave) and/or with another ECG abnormality which in the opinion of the study physician is clinically significant and represents a safety risk. Note that if the initial QTc value is prolonged, the ECG should be repeated two more times (with 5 minutes between ECG readings) and the average of the 3 QTc values used to determine eligibility.

18. Clinically significant head injury (e.g., requiring medical or surgical intervention) that in the opinion of the investigators, contraindicates their participation .

19. Active hepatitis or HIV.

20. Active peptic ulceration.

21. Significant current or past medical history that, in the opinion of the investigators, contraindicates their participation.

22. The subject has participated in a clinical trial and has received an investigational product within 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) prior to the first experimental visit.

23. Pregnancy or breast-feeding

24. Unwillingness or inability to follow the procedures outlined in the protocol.

7 RISKS AND BENEFITS

7.1 Ethical considerations

The Chief Investigator will abide by the ethical principles underlying the Declaration of Helsinki (1996) and good clinical practice (GCP) guidelines on the proper conduct of research, and comply with research governance.

Investigators will hold honorary contracts or research passports, will be trained in GCP, Data Protection, GDPR and will hold current DBS checks. The team includes clinically experienced addiction staff who can immediately deal with any issues arising from this study, as well as link with support from the clinical teams managing the clinical care of opiate dependent participants.

All opiate dependent participants will be engaged with a specialist clinical service for their community based detoxification. They will therefore be receiving support and know how to access extra support if required. The risk of relapse to on-top opiate use is a common challenge faced by individuals in this indication. However, significant instability is less likely in those who are on stable doses of methadone, or those who are tapering or preparing to undertake detoxification. Further, if an individual feels they may relapse, additional support is provided and reduction in their methadone is generally suspended. In this case, we would wait until the risk of on-top use was reduced and their stability or gradual reduction in methadone dose was resumed. The clinical team will have the opportunity to raise with the research team if there are concerns about any participants' suitability to take part in the study or change in circumstance post-screening. Further the PI, Prof Anne Lingford-Hughes is a Consultant addiction psychiatrist with over 20yrs experience in this field and the research team also have several years' experience working with this population.

7.1.1 Potential Risks

No treatment is withheld from participants in this study and testing will be performed at times convenient to all persons.

Some participants may find the long experimental study day tiring. We will endeavour to take all steps to ensure comfort and provide appropriate rest and sustenance during these procedures.

In our previously completed study (Durant et al 2018) a few of our healthy volunteers and abstinent alcohol dependent individuals reported minor side effects to the 60mg dose of baclofen, primarily dizziness and, nausea. These side effects resolved and all participants were fit to be discharged by end of the study day. The 90mg dose resulted in more pronounced sedation in one healthy volunteer with mild effects still felt the following day so we did not proceed with testing any further healthy participants at this dose. No such effects were seen in the alcohol dependent group and no significant

cardiovascular effects (e.g. blood pressure, heart rate) were observed in either group. The model in this proposal will mitigate risks of giving such high doses if sedation is seen at lower baclofen doses.

We are carefully monitoring for any signs of respiratory depression and such information will be utilised in the model to determine the next safe dose combination. We have enhanced assessments of possible respiratory impairment in our screening protocol so that anyone at risk of respiratory depression is excluded.

7.1.2 Potential Benefits

Research participants will not directly benefit from taking part but the information we get might help improve the treatment of people with opiate dependence in future.
Participants will receive feedback if requested about all aspects of the study, but this will not be available until the end of the study as this is a research investigation and the clinical relevance of the measures taken is not proven.

8 STATISTICS AND DATA ANALYSIS PLAN

8.1 General statistical principles

No formal statistical testing will be conducted for this early phase study and no power calculation has been peformed; all statistical analyses for primary and secondary outcomes are to be viewed as exploratory.

8.2 METHODS OF RANDOMISATION

The randomisation schedule will be generated by Sealed Envelope, or independent statistician, using a 3:1 ratio (baclofen: placebo). Blocked randomisation will be used maintain the 3:1 ratio throughout the study.

8.2 SAMPLE SIZE

The sample size in Phase I is not fixed. Up to a total of 64 patients are planned to be enrolled in the study with up to 48 patients on the experimental baclofen doses and 16 on placebo with a 3:1 allocation ratio. The final sample size will depend on the escalation/de-escalation decisions made using the trial and on the recommendation of the model on stopping earlier. The performance of the Bayesian design based on 48 participants was assessed via simulations under several clinically relevant scenarios in terms of accuracy of the number of patients that would receive (i) their individual target dose combination and (ii) a combination that is safe for them in the subsequently planned phase 2 trial.

8.3 STATISTICAL ANALYSIS PLAN

8.3.1 Analysis sets

8.3.1.1 Full analysis set

The full analysis set includes all randomised patients. This is equivalent to the ITT (intent-to-treat) population. The Full analysis set will be used to summarise study conduct and patient disposition.

8.3.1.2 Safety set

The safety analysis set will consist of all subjects who are randomised and received study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries. Patients will be grouped according to actual treatment received.

8.3.1.3 DLT evaluable safety set

The DLT evaluable safety analysis set will consist of all subjects who are randomised and received study drug and are evaluable for a DLT. Subjects in this analysis set will be used for the primary dose-combination toxicity response analysis (included in the Bayesian analysis model). Patients will be grouped according to actual treatment received.

The analysis set for each secondary outcome will be based on the subset of patients from the safety set for whom at least 1 measurable outcome has been obtained.

8.3.2 Primary analysis

The first phase I cohort (4 patients) will be randomised to 10mg of baclofen or placebo (3:1 allocation ratio) with subsequent planned dose escalation of baclofen up to 90mg. The escalation will occur only in the case of acceptable safety and tolerability at the next lowest dose of baclofen for the prescribed dose of methadone and if no DLTs are observed for the current cohort of patients. Doses of baclofen cannot be skipped. The relationship between the doses of baclofen and methadone and the probability of observing a DLT will be modelled via a 5-parameter Bayesian logistic regression model with an interaction parameter (Neuenschwander B, 2015). The model will be sequentially updated after at most every 3 patients using the DLT/no DLT data from all previous cohorts in the trial before making the recommendation for the next cohort.

Dose escalation will be based on the review of safety data during the experimental visit on the DLT evaluable safety set. For each given patient with a prescribed dose of methadone, the doses of baclofen are deemed to be safe if the risk of dose-limiting toxicity (DLT) being at least 25%, is less than 25%. The recommendation of the model will be to assign patients in the next cohort to their individual safe doses of baclofen that are more likely to have a toxicity risk of between 15% and 25% according to their prescribed dose of methadone (subject to the escalation constraints above). The patients in the next cohort can receive different doses of baclofen depending on their individual doses of methadone and previous data contributing to the model.

The model can recommend stopping the trial earlier with all doses of baclofen found to be safe, if the probability that the risk of toxicity at 90mg baclofen in combination with 120mg methadone is 25% or below, is above 92.5%. The trial can be recommended to be stopped earlier for safety concerns if the probability that the risk of toxicity at 30mg baclofen in combination with 60mg methadone (the lowest clinically viable combination) being above 25%, is 25% or more.

Further details of the specification of the 5-parameter Bayesian logistic regression model are provided in the detailed Statistical Analysis Plan (SAP) that will be agreed by the TSC.

The DSC can over-rule the recommendation of the model in the light of other safety and tolerability information.

The primary statistical analysis will be conducted in R software.

8.3.3 Secondary analysis

Descriptive statistics (means/medians, with min/max and SD/IQR or frequencies and % as appropriate for the data distribution) will be presented for each secondary outcome by time point and treatment group. Secondary outcome measures will also be presented graphically over time and treatment group using appropriate summary statistics for the data distribution.

Descriptive statistics will be also presented for secondary outcomes by baclofen dose and gender. Correlation analyses, using Pearson or Spearmaks rank correlation

coefficient, will be conducted to explore the associations between outcomes and methadone dose.

For repeated continuous measures linear mixed models may be used to explore the effects of time and group (placebo versus baclofen). Where data allows, linear mixed models may be extended to explore the effects of baclofen dose and methadone dose on secondary outcomes.

Secondary outcome analysis will be conducted using SPSS, Stata or R software.

8.3.4 Analysis of GABA-B sensitivity outcomes

Analysis of PK/PD endpoints to determine GABA-B sensitivity will be analysed as previously described (Durant et al, 2018).

8.3.5 Analysis of exploratory outcomes

An assessment of sources of variability e.g. age, dose on PK-PD and safety outcomes will be made. These exploratory analyses will be described in more detail elsewhere.

8.3.6 Adverse events

Adverse events will be tabulated by treatment group (baclofen versus placebo). Where useful a time to event analyses will be undertaken to depict the timing of adverse events (using hazard plots) and display the difference in time to event curves between treatment groups (baclofen versus placebo) and baclofen dose group for comparative purpose.

8.3.7 Missing data

Every effort will be made to obtain all follow up data for all participants. Data summarises will be based on observed data only. Linear mixed model analyses employ maximum likelihood estimation and thus are efficient for handing missing outcome data under a missing at random (MAR) assumption.

A detailed statistical analysis plan, which will describe the primary and secondary analyses of the trial will be developed and agreed by the TSC.

9 DATA AND STUDY MANAGEMENT

9.1 Data Monitoring & Interim Analyses

A DMC will be convened and meet regularly to discuss study progress, recruitment targets and future planning. If a trial stopping rule was triggered a DMC meeting would be convened to review the TMG's decision to stop/continue the trial.

Quality control checking and introduction of improvement procedures for data analysis will be ongoing throughout data collection. The study uses the continual reassessment method to assess the dose-toxicity response. There is no formal plan for interim data analysis of secondary outcomes before the completion of the study, however data will be continuously monitored to determine whether data collection should continue as planned, or be targeted towards a particular demographic or methadone dose to increase precision in secondary outcomes.

9.2 Direct Access to Source Data & Documents

In the event of an audit or study related monitoring procedure, where source documents and data has to be reviewed, the chief investigator will permit study related monitoring, which will require access to source data or documents.

During the study, it will only be the Chief Investigator, the co-investigators, as well as the rest of the research team involved in the study, who will have access to data produced by the study.

9.3 Data handling and record keeping

This study and its staff will be compliant with the Data Protection Act and GDPR with regards to the collection, storage, processing and disclosure of personal information. It is under the Chief Investigator's responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register, when necessary, with the appropriate Data Protection Officer.

The study team will complete a Data protection impact assessment (DPIA) according to data protection legislation to identify how the study will process and store data and to identify and minimise data protection risks.

9.3.1 Personal data

Personal contact details are required for communication with the subjects participating in the study. This information is held solely for communication between the researchers and participants.

Information held on NHS computers is solely for the purpose of hospital booking and routine sample collection and analysis (e.g. for medical screening). This information is password protected in a similar manner to that of other hospital patients. Access to additional patient records is explicitly requested from participants and this is made clear in the Information/Consent forms.

Each participant will be identified by a unique code number that will be used throughout the duration of the study. Participant names, addresses, and other contact details will be written in the clinical screening portion of the paper-based CRF for identification and contact purposes. The clinical screening CRFs will be regarded as confidential, and kept in locked filing cabinets in Imperial College. The contact details will then be removed from the CRF and into participant notes for storage.

Only the CI, and selected study team members will have access to anonymised codes and their link to personal ID. This will be kept locked in a file on site and electronically on secure servers accessed by research team members only (password protected).

9.3.2 Study data management

All data will be collected in a pseudonymised and coded manner and stored within paper-based CRFs and/or via electronic data capture (EDC) within purpose built secure-access online databases; OpenClinica and REDCap, or saved electronically on secure University (Imperial College) computer systems and facilities. This will ensure

the safe acquisition, storage and transmission of data. University computers and servers are all password protected and study data can only be accessed by the researchers involved in the study.

Quality control will be conducted according to ICTU, OpenClinica, REDCap or FORWARDS study SOPs, as appropriate.

9.3.3 OpenClinica

The electronic data capture (EDC) system for collecting and entering data is OpenClinica on an all-in-one platform. It is fully validated and compliant with 21 Code of Federal Regulations (CFR) Part 11 - Electronic Records; Electronic Signatures. The EDC system is also ICH-GCP and ISO9001 compliant.

The Imperial College Clinical Trials Unit (ICTU) will be responsible for study control; from eCRF design to study close-out; database build and system validation while OpenClinica Cloud will be responsible for hosting the data. The trial specific OpenClinica system is built from requirements defined by the Chief Investigator, Trial Statistician and Study Manager and approved by the Chief Investigator. eCRF design documents and all approvals will be filed in the Trial Master File (TMF). The OpenClinica system will be built with data validation, automatic queries, alerts and edit checks as defined in the study requirements.

The system is capable of real-time data entry for rapid access such that the Dose Setting Committee can make timely updates to the adaptive Bayesian model after (at most) every baclofen group of 3 participants.

Access permissions to OpenClinica will be managed by ICTU according to the trial requirements and SOPs. Data entry will be managed according to ICTU and FORWARDS SOPs.

9.3.4 REDCap

Exploratory outcomes will be captured using REDCap (Research Electronic Data Capture) tools hosted at Imperial College London (PA Harris, 2019, 2009). REDCap is a secure, web-based software platform designed to support online or offline data capture for clinical research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

REDCap can be used to capture a variety of types of data including 21 CFR Part 11, FISMA and HIPAA compliant environment.

9.3.5 Custodian of the Data

The CI, Professor Anne Lingford-Hughes, will be custodian of the data.

9.3.6 Format of Records

Personal data and raw data formats will be stored in patient hospital notes, paper-based CRFs or on password protected computer systems within the study sites, as appropriate.

Screening data will be pseudonymised where possible, and stored in paper-based or eCRFs, as appropriate.

Study data will be pseudonymised and stored in paper-based or eCRFs, as appropriate.

9.3.7 Duration & Location of stored data

Primary research data / records will be retained in their original form for a minimum of 10 years after the study has been completed.

Location of data: Data will be stored within paper-based CRFs according to local security procedures, electronically on secure University (Imperial College) computer systems and facilities or within purpose built secure-access online databases, OpenClinica and Redcap, as detailed above.

9.4 Training and User Support

All staff employed on the grant and all Investigators will be trained in:

- GCP
- Use of the assessment tools
- Study standard operating procedures
- Use of Study databases (OpenClinica & REDCap)

All staff working directly with participants will have a CRB check, a License to attend (or equivalent) for the ICRF, and an honorary contract (or research passport) with Central and North West London (CNWL) NHS trust.

10 ADVERSE EVENT REPORTING

10.1 Adverse Events and Adverse Reactions

10.1.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Unexpected Adverse Reaction: an AR, the nature or severity of which is not listed in the reference safety information (RSI) e.g. list of expected medical events within investigator's brochure for an unapproved investigational product or section 4.8 of the summary of product characteristics (SmPC) for an authorised product. *When the outcome occurs this adverse reaction should be considered as unexpected. Side effects*

documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.

Serious Adverse Event (SAE) or **Serious Adverse Reaction:** any untoward medical occurrence or effect that at any dose:

- **Results in death.**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation.**
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly or birth defect.**

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

10.1.2 CAUSALITY

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).

Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

10.1.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

10.1.4 NON SERIOUS AR/AES

All such toxicities, whether expected or not, should be recorded in the toxicity section of the relevant case report form and sent to the study coordination centre within one month of the form being due.

10.1.5 SERIOUS AR/AES

Fatal or life threatening SAEs and SUSARs should be reported on the day that the local site is aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

SAEs

An SAE form should be completed and sent to the study coordination centre for all SAEs within 24 hours. OpenClinica software facilitates notification of the SAE form via email. However, relapse and death or hospitalization due to substance use disorder that cannot reasonably be attributed to study medication, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

SUSARs

In the case of suspected unexpected serious adverse reactions, the staff at the site should:

Complete the SAE case report form & send it immediately (within 24 hours,), signed and dated to the study coordination centre together with relevant treatment forms and anonymised copies of all relevant investigations.

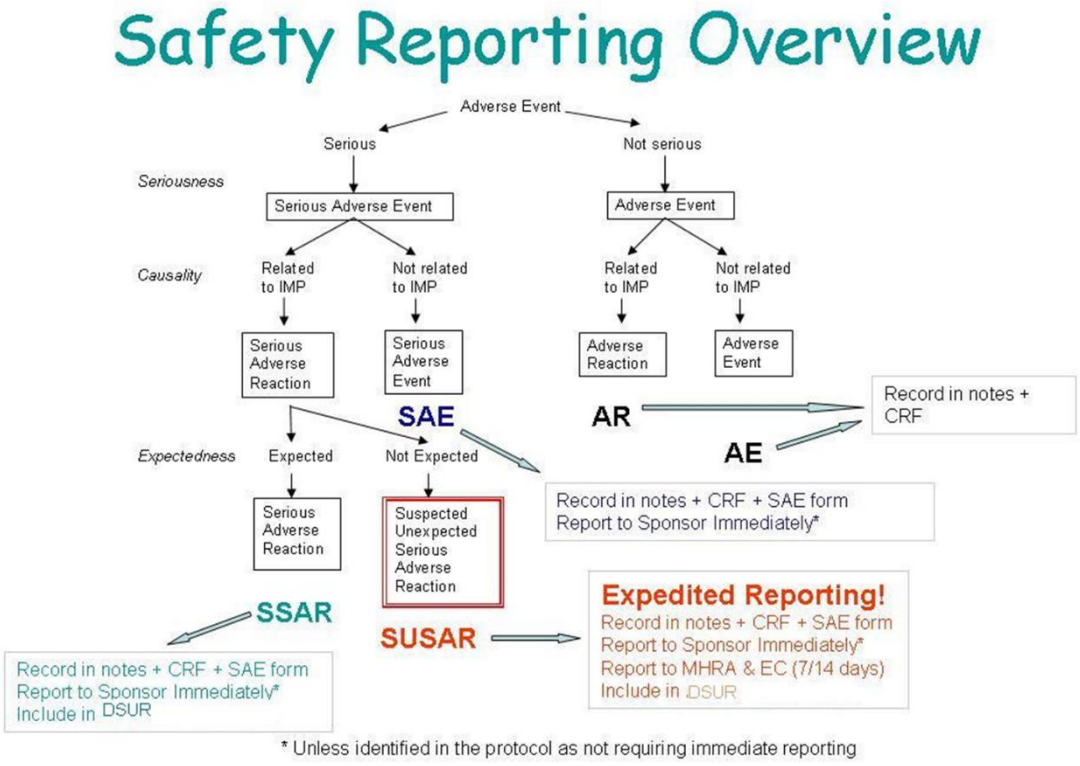
Or

Contact the study coordination centre by phone and then send the completed SAE form to the study coordination centre within the following 24 hours as above.

The study coordination centre will notify the MHRA, REC and the Sponsor of all SUSARs occurring during the study according to the following timelines; fatal and life-

threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study.

Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.



10.2 Contact details for reporting SAEs

Contact details for reporting SAEs
jrco@imperial.ac.uk

CI email (and contact details below)
Prof Anne Lingford-Hughes
Please send SAE forms to: anne.lingford-hughes@imperial.ac.uk
Tel: 020 7594 8682 / Fax: 020 7594 6548
PA: Nicole Hickey – n.hickey@ic.ac.uk, Tel: +44 (0)20 3313 4161

11 REGULATORY ISSUES

11.1 CTA

This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA.
EudraCT number: 2021-002556-36

11.2 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the West of Scotland REC 1 Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

11.3 COMBINED WAYS OF WORKING

This study will be using the Combined Ways of Working Pilot scheme in order to obtain approvals from: MHRA, REC and HRA.

11.4 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

11.5 CONFIDENTIALITY

Participants' identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. However, should there be any concerns about risks of harm to the participants or anyone else, a clinical decision will be made with regard to disclosure of information and appropriate support will be discussed with the participant.

11.6 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study

11.7 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

11.8 FUNDING

This study is funded by the Medical Research Council, grant number MR/T025557/1 (Infoed- P86340). Participants will receive compensation for taking part in the research. They will receive £50 for screening and £100 for a completed experimental visit, received either by bank transfer, or vouchers (as requested).

11.9 AUDITS AND INSPECTIONS

The study may be subject to inspection and audit by Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

11.10 Publication policy

It is intended that the results of the study will be reported and disseminated in peer-reviewed scientific journals, and internal reports, conference presentations, written feedback to study participants and consultants, and presentations to relevant community groups.

11.11 Protocol amendments

None

12. TRIAL MANAGEMENT

A Trial Management Group (TMG) has been appointed to oversee the FORWARDS grant in its entirely and meet regularly to monitor milestones and targets and will be responsible for overseeing the progress of the trial.

A DMC and TSC will additionally be convened for oversight of trial & data management.

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigator and Trial Manager. The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

A fully independent Data Monitoring Committee (DMC) will be set up to monitor progress, participant safety, and any ethical issues involved in this trial. They will review trial progress, recruitment rates, safety, and data emerging from other trials and make recommendations to the TSC as to whether there are any reasons why the trial should not continue. The DMC membership will include independent experts in addiction and/or pharmacology and/or physiology and a clinical trials statistician. A separate DMC Charter will be drawn up defining their responsibilities, frequency of meetings and reporting to the TSC. The DMC are permitted to have access to the unblinded data for review and any comparisons between groups where appropriate.

The Dose Setting Committee (including a statistician, clinician and member of the research team) will be responsible for regular review of data relevant to the updating of the model (incidence of DLT). The trial statisticians will be responsible for the updating of the adaptive model.

The day-to-day management of the trial will be co-ordinated by the research team.

13. STUDY MONITORING

Study Monitoring at Imperial College NHS foundation trust will be conducted by the RGIT Clinical Trials Monitor and overseen by the RGIT Clinical Trials Manager or delegate, according to their SOPs.

Monitoring undertaken at other research sites e.g. CNWL sites, will be undertaken by the research team under the responsibility of the Chief Investigator (CI) or Principal Investigator (PI) who will make appropriate monitoring arrangements. The Monitors will be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. Training records, including relevant qualifications, will be kept by the monitor and checked by the Chief Investigator.

The monitor will be familiar with the Investigational Medicinal Product (IMP), the protocol, information sheet and consent form, as well as the Imperial College AHSC SOPs, GCP and applicable regulatory requirements

13.1 RISK ASSESSMENT

A Monitoring Risk Assessment will be conducted in relation to the Colleges SOPs identifying the level of risk involved with this study.

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