TRIAL PROTOCOL

DEXTA

DEXmedetomidine Trial of Adjunct Treatment with Morphine

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CI and Sponsor Approval Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol, and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, Nottingham Clinical Trials Unit (NCTU) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

This protocol has been approved by:	
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Amendments

Amendment number	Protocol version number	Type of amendment	Summary of amendment

Abbreviations

Abbreviation	Term
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CEA	Cost Effectiveness Analysis
CI	Chief Investigator
CPAS	Cancer Chemotherapy and Pharmacy Advisory Service
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
CUA	Cost Utility Analysis
DAP	Data Analysis Plan
DMC	Data Monitoring Committee
DoR	Delegation of Responsibilities
DSUR	Development Safety Update Report
EC	European Commission
eCRF	Electronic Case Report Form
EMEA	European Medicines Agency
EoT	End of Trial
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCTE	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
IB	Investigator's Brochure
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare Products Regulatory Agency
MS	Member State
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NIMP	Non-Investigational Medicinal Product
PD	Pharmacodynamics
PI	Principal Investigator

PIC	Participant Identification Centre
PIS	Parent Information Sheet
PK	Pharmacokinetics
PMA	Postmenstrual Age
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Relevant Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Products Characteristics
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

Trial Summary

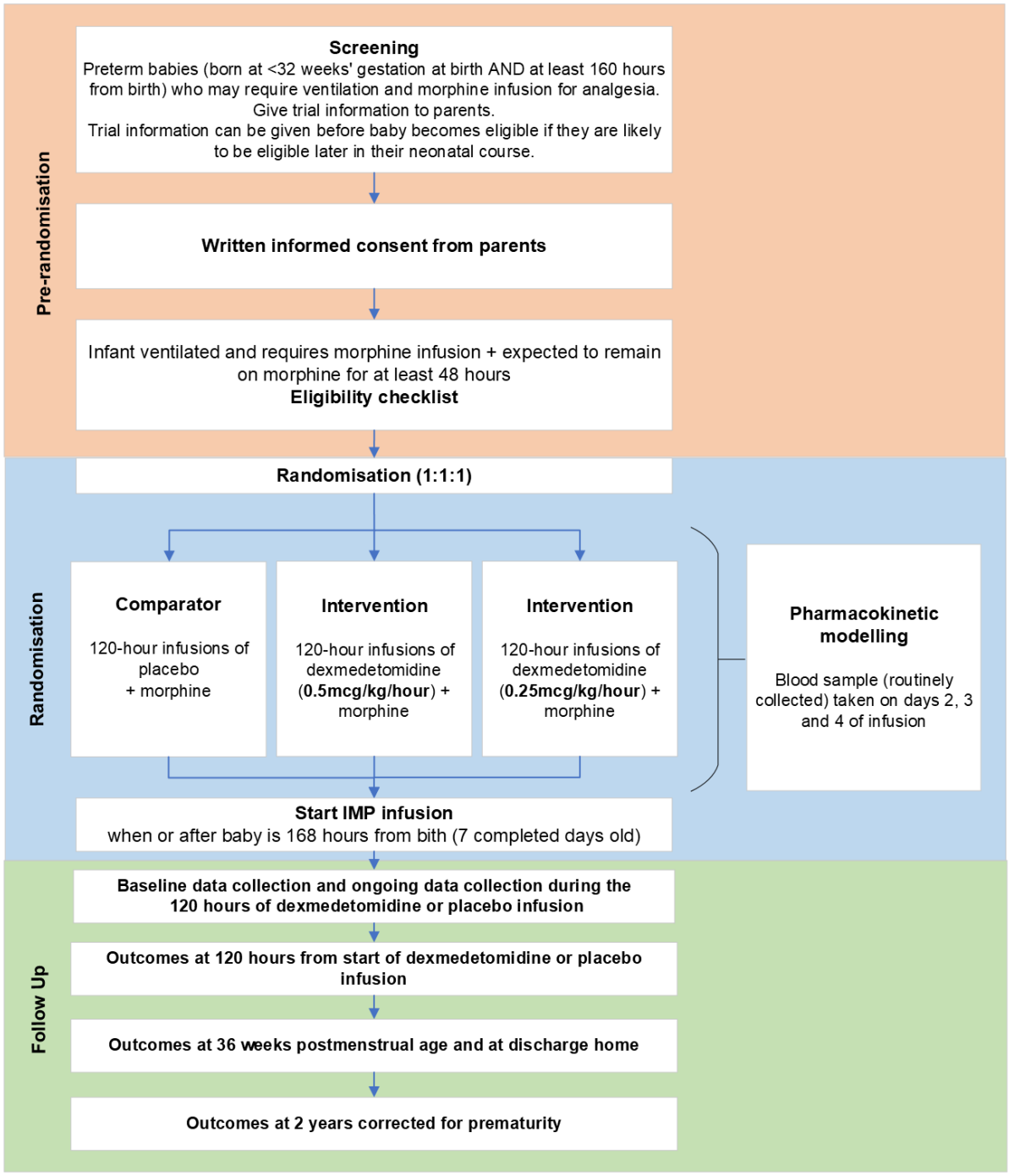
Trial Title	DEXmedetomidine Trial of Adjunct Treatment with Morphine	
Short Title	DEXTA	
Clinical Phase	Clinical trial of investigational medicinal product (phase IV) Medicines and Healthcare Products Regulatory Agency (MHRA) Type B	
Objectives		**Outcome Measures**
Primary	To determine if, in ventilated preterm babies, dexmedetomidine is efficacious in reducing the cumulative dose of morphine given over 120 hours from starting the dexmedetomidine or placebo infusions	Cumulative dose of morphine given over 120 hours from starting the dexmedetomidine or placebo infusion
Secondary	To investigate the potential benefits and safety of dexmedetomidine, given with morphine infusion on: - pain - total duration and additional doses of morphine - duration of ventilation and intensive care - time taken to reach full milk feeds - bronchopulmonary dysplasia - preterm brain injury - bradycardia - hypotension	**Over 120 hours from start of infusion:** - pain (measured by standardised preterm pain scale) - total duration of morphine infusion (hours) - use of additional morphine bolus - total additional morphine (in microgram/kg and number of additional boluses) - morphine and dexmedetomidine total drug exposure integrated over time (Area Under the Concentration Time Curve (AUC)) - total dose and duration of other analgesics - total duration of ventilation (hours) - number of episodes of bradycardia requiring intervention - heart rate (assessed hourly) - blood pressure (every two hours) - Oxygen saturation (assessed hourly) - FiO_2 (assessed hourly) - requirement of additional vasopressor support **At discharge from neonatal care:** - preterm brain injury - time to reach at least 140 ml/kg/day full milk feeds (in hours) after randomisation - bronchopulmonary dysplasia

		- length of intensive, high-dependency, and total neonatal care (days) - parent experience (self-reported questionnaire) - late onset infection – microbiologically confirmed - necrotising enterocolitis (Bell's Stage 2 or 3) - retinopathy of prematurity - death
	To compare neurodevelopmental outcomes between groups at 2 years of age corrected for prematurity	**Long-term outcomes:** Survival without moderate or severe neurodevelopmental impairment at 2 years of age corrected for prematurity including visual, hearing, gross motor, cognitive and language impairments
	To determine whether there is an imbalance in dexmedetomidine or morphine exposure resulting from inter-individual variability in clearance	Dexmedetomidine and morphine cumulative Area Under the Curve (AUC) derived from dose history and plasma samples of dexmedetomidine and morphine concentration over time
	To determine if, in ventilated preterm babies, dexmedetomidine is efficacious in reducing the cumulative AUC of morphine over 120 hours from starting the dexmedetomidine or placebo infusion	Cumulative morphine and dexmedetomidine AUC derived from dose history and plasma samples of dexmedetomidine and morphine concentration over time
Exploratory	To quantify the relationship between dexmedetomidine concentration and haemodynamic markers (heart rate and blood pressure)	PKPD model derived from dose history and plasma samples of dexmedetomidine and morphine concentration over time and heart rate/blood pressure measurements
	To quantify the relationship between dexmedetomidine concentration and pain score	PKPD model derived from dose history and plasma samples of dexmedetomidine and morphine concentration over time and pain scores
Trial Design	A three-arm, multicentre, blinded, randomised placebo-controlled, efficacy trial with a superiority hypothesis testing framework, a built-in safety run-in period, and planned single interim analysis with integral Pharmacokinetic-Pharmacodynamic (PKPD) analysis	
Trial Participant Population	Ventilated preterm babies (<32 weeks' gestational age at birth) who are at least 160 hours from birth and require morphine infusion for analgesia	

Setting	Fifteen UK Neonatal Intensive Care Units
Key Eligibility Criteria	**Inclusion Criteria** - <32 weeks' gestational age at birth AND at least 160 hours elapsed from birth - expected to require at least 48 hours of ventilation from randomisation - receiving/requiring morphine infusion
	Exclusion Criteria - mother has received any opiates during pregnancy (excluding during labour) - baby: o has major congenital anomaly o is haemodynamically unstable despite receiving two or more inotropes o is highly likely to be transferred to another hospital within 5 days of randomisation o has no realistic prospect of survival (as judged by the clinical team) o contraindicated to Dexmedetomidine as per the local SmPC o history or evidence of any other medical condition that would expose the participants to an undue risk of a significant AE or interfere with study assessments during the course of the trial (as determined by the clinical judgment of the investigator)
Sample size estimate	Sample size is based on two related primary comparisons (each dose of dexmedetomidine vs placebo comparator, respectively) with a planned single interim analysis for futility (at half of the planned maximum sample size). A maximum of 60 babies per group are needed to detect a 30% reduction in the geometric mean cumulative dose of morphine over 120 hours (equivalent to a ratio of geometric means of 0.7) between a dexmedetomidine and the placebo comparator group, with 90% marginal power and 5% one-sided family wise error rate. The primary analysis population will include babies who receive at least 48 hours of trial infusion, so the sample size has been inflated to a maximum of 240 randomised babies if both doses continue to the end of the trial, (potentially 80 per group) to allow for premature discontinuation of the trial drug in some randomised babies.
Number of participants	A maximum of 240 babies (80 per group)
Treatment duration	120 hours
Follow up duration	Until 2 years of age corrected for prematurity
Planned Trial Period	Overall trial duration is 66 months (start date 1 Nov 2024 and end date 30 Apr 2030)
Investigational Medicinal Product(s) and comparator group	Intervention 1 – 120-hour infusions of dexmedetomidine (0.5microgram/kg/hour) + morphine

	OR Intervention 2 – 120-hour infusions of dexmedetomidine (0.25microgram/kg/hour) + morphine OR Comparator group – 120-hour infusions of placebo + morphine
Randomisation and blinding	Babies will be randomised individually in a 1:1:1 allocation ratio using a probabilistic minimisation algorithm balancing on the following factors: recruiting site, gestational age at birth, sex, postnatal age and any previous morphine exposure since birth. Randomisation will be provided through a secure online randomisation system developed and hosted by Nottingham Clinical Trials Unit (NCTU), University of Nottingham. If recruitment to one of the active doses of dexmedetomidine arms is stopped following the interim analysis, randomisation will continue to the remaining options using a 1:1 allocation ratio. To mask the identity of the trial interventions (i.e., maintain the blinding of allocation), dexmedetomidine and placebo ampoules will be identical in appearance and packaged in blinded participant kits.
Statistical methods	Analysis and reporting of the trial will be in accordance with CONSORT extensions for multi-arm trials and adaptive designs. Analysis will be according to randomised allocation with the primary analysis population including babies who receive at least 48 hours of trial infusion. Log-transformed cumulative morphine dose will be analysed using a mixed effects linear regression model, adjusting for gestational age and, where technically possible, the other minimisation factors. A single interim analysis will be conducted to potentially allow one or both doses of dexmedetomidine to be stopped for futility, at half of the planned maximum sample size. All analyses will be specified in the Statistical Analysis Plan and finalised prior to the interim analysis.

Trial Flow Chart



1. Background and Rationale

1.1. Background

Pain in preterm babies is inadequately managed and under-researched (1). Morphine is frequently used for analgesia during ventilation as it is painful (2,3). However, evidence suggests that morphine may not provide adequate analgesia and may adversely prolong the need for ventilation and time to reach full milk feeds (4–6). Additionally, babies given larger doses of morphine in early life have a higher risk of brain injury and poorer neurodevelopment and behavioural outcomes in later life (7–9). Despite this, due to lack of alternatives, morphine continues to be the most popular analgesic for ventilated babies (2,3).

Dexmedetomidine is an alpha-2 adrenergic receptor agonist that provides analgesia without sedation (10). It is an alternative to morphine in adult and paediatric intensive care. Some observational studies found that it can reduce the dose of morphine needed to provide analgesia in babies (10). It is not currently used in UK neonatal practice. There are no completed or ongoing randomised trials investigating its use in ventilated preterm babies (11).

1.2. Trial Rationale and Justification of Design

Adequate pain relief is fundamental to good intensive care, yet pain in preterm babies is often inadequately managed (1). Ventilation is invasive and painful. Pain is exacerbated by both procedures and underlying diseases (1,4). Pain interferes with the ventilator synchronising with the baby's breathing leading to suboptimal ventilation, fluctuations in heart rate, respiratory rate, blood pressure, and oxygen saturation and complications such as intraventricular haemorrhage (12). The optimal management of pain in ventilated preterm babies remains unclear. Morphine is widely recommended (1,13) and is popular despite lack of evidence of benefit (4) and associations with harm (8). In EUROPAIN, a prospective audit of ventilated babies in 243 European Neonatal Intensive Care Units, morphine and fentanyl (another opioid) were given to 923 (43%) and 639 (29%) babies, respectively (2). The percentage of babies <32 weeks' gestational age receiving morphine increased from 32% in 2010 to 37% in 2017 (14), reflecting a lack of effective and safe alternatives. Moreover, results of studies investigating long-term effects implicate a dose-response relationship with harm (8). Exposure to low doses of morphine for pain is not associated with poor development but higher cumulative doses and longer durations of use lead to poor cerebellar growth, cognitive and motor outcome (7,8).

Analyses of data held in the National Neonatal Research Database (3), which includes data from all neonatal units in England and Wales identified preterm brain injury (defined as presence of severe intraventricular haemorrhage, periventricular leukomalacia, or post-haemorrhagic ventricular dilation at 36 weeks' postmenstrual age (15)) in 7,698/24,815 (31.0%) babies who were ventilated for >2 consecutive days. This included 6,699/20,561 (32.6%) who received an opioid during ventilation and 999/4,254 (23.5%) who did not. Propensity scored matching showed that the odds of preterm brain injury was higher in those who received opioids (received opioids, 990/3,608 (27·4%) vs. 855/3,608 (23·7%); odds ratio 1·22, 95% confidence interval [CI] 1·10 to 1·35). In the matched cohort, the odds of more severe grades of brain injury and the composite outcome of brain injury or death, were also higher in those who received opioids. The odds of these adverse outcomes increased with increasing exposure to morphine: the adjusted odds of preterm brain injury, severe grades of brain injury, and the composite outcome of brain injury or death increased significantly with increasing number of days of exposure to opioids during ventilation[11]. In comparison to those who did not receive opioids, the adjusted odds (95% CI) of brain injury or death was 1.18 (1.05 to 1.34) in those who received it for 3 days, 1.26 (1.10 to 1.45) in those who received it for 4 days and 1·42 (1·22 to 1·65) in those who

received it for 5 days. The analyses could not determine the effect of exact cumulative doses on brain injury as dosage data are not available in the database.

Although it is possible that babies who need opiates for longer are more unwell and therefore more likely to have complications, these findings are supported by other studies showing that those who receive higher doses are more likely to have worse neurodevelopmental outcomes. Kocek et al., found, in a cohort of 100 babies born at <1,000g birth weight, that even after adjusting for birthweight, gender, insurance status, and co-morbidities each 1 mg/kg increase in cumulative dose of morphine was associated with 0.25-point decrease in cognitive score at 20 months of age corrected for prematurity (9). Similarly, Lammers et al., reported that in 147 babies born at <1,500g birth weight, that for every 1microgram/kg increase in the cumulative dose of fentanyl, both cognitive and motor skills worsened and those who received more than 7 days of fentanyl had a lower motor score compared to those who received a lower dose (16). Increase in cumulative opioid exposure is also associated with behavioural disorders in later childhood. Steinbauer et al., found that each 100mg/kg increase in opioid exposure was associated with increased risk of autistic spectrum and features of social withdrawal at preschool age (17).

In 2009, health economic analyses showed that the cost of preterm birth to the public sector was £2.95 billion with a £94,740 incremental cost for each extremely preterm baby who survives to adulthood (18). These costs are higher in those who suffer brain damage and need additional health, social, and educational support. Both untreated pain and large doses of morphine to treat pain in early life add to this burden by worsening the risk of brain damage.

Thus, the optimal approach to provide analgesia would be to use the smallest dose of morphine. For this, we must investigate new drugs, such as dexmedetomidine, which could provide analgesia while reducing morphine exposure. New analgesics that optimise pain relief while minimising adverse effects of morphine are desperately needed.

1.2.1. Justification of the Participant Population

This study will include babies who are born at <32 weeks' gestational age and need mechanical ventilation. It will include babies who are >7 days old because, when born at <32 weeks' gestational age, babies have immature liver function and the metabolism of dexmedetomidine may be too slow. Liver enzymes do, however, mature after birth and evidence from full term infants shows that dexmedetomidine clearance is diminished initially and rapidly in the first weeks reflecting the immaturity of the metabolic processes in the newborn period (19).

In the UK, over 100,000 babies need specialist neonatal care each year (1 in 7 live births). Respiratory illness necessitating ventilatory support is the most common pathology requiring intensive care. Babies born at <32 weeks' gestational age are the most likely to need ventilation. Analyses of the National Neonatal Research Database (3)data between 2012 and 2020 show, in England and Wales a median (interquartile range [IQR]) of 7,600 (7,229 to 7,762) babies less than <32 weeks' gestational age were admitted each year to neonatal units, of which 68% (median 5,183 (IQR 4,837 to 5,299)) were ventilated including 37% (median 2,826 (IQR 2,665 to 2,868)) who were ventilated for more than 48 hours. The median (IQR) duration of ventilation was 4 (3 to 12) days.

These analyses show that 58% of the babies <32 weeks' gestational age who were ventilated received morphine, which was given on two-thirds of ventilated days (3). This widespread use is despite a lack of evidence. The 2021 Cochrane review concluded that there is uncertainty whether morphine reduces pain in ventilated babies (4) and there are concerns about short and long-term adverse effects. This uncertainty is reflected in the variation in practice: among the 175 UK neonatal units that contribute data to the National Neonatal Research Database, use of morphine on the days when a baby was ventilated ranges from 9% to 80% of ventilated days in different units (3).

Preterm babies age is measured from their birthdate or from their estimated date of conception to accommodate for their prematurity. Gestational age (GA) is the number of weeks of pregnancy when the baby was born. Post menstrual age (PMA) is the number of weeks since conception. It includes the gestational age at which the baby was born and the age since birth. Age corrected for prematurity or Corrected age is the age the baby would now be, had they been born at 40 weeks of the pregnancy.

1.2.2. Choice and Rationale of Experimental Treatment

Dexmedetomidine is a potential, novel alternative that could reduce the absolute amount of morphine used for analgesia in preterm babies (10,20–23). It was approved for use in adult intensive care in 1999 by the USA Food and Drug Administration and the European Medicine Agency (24). It provides analgesia by inhibiting substance P release from the dorsal horns of the spinal cord and anxiolysis/sedation by reducing sympathetic outflow from the locus coeruleus (21). It induces brain activity similar to non-rapid-eye-movement sleep, mimics natural sleep and maintains spontaneous breathing and upper airway tone (22).

It is not currently used routinely in preterm babies in the UK (3,14). If found to be efficacious and safe in providing analgesia and reducing the use of morphine in preterm babies, its use could improve short and long-term outcomes with a reduced negative impact on the developing brain. The subsequent improved childhood developmental and behavioural outcomes would reduce burden on families, costs to the NHS, social and education services, and improve the broader health of the nation.

A scoping review of use of dexmedetomidine in ventilated preterm babies (25) found that several publications have reported its use, including preterm babies in the first weeks after birth and at later age (20,21), in term-born babies following surgical procedures (26,27), during therapeutic hypothermia (21,28,29) and for procedures such as magnetic resonance imaging (30,31). In neonatal care in the USA (2010 to 2018) dexmedetomidine was ninth among drugs that had the greatest relative increase in use, and it was the 90th most frequently prescribed drug (32). In a 2023 survey of 225 European neonatal units, only one reported that they use dexmedetomidine as first line therapy, while 15 said that they use it as an add-on to opioids (33).

1.2.3. Justification for the choice of route of administration, dosage, dosage regimen, and treatment period

Dexmedetomidine use is well established in adults and increasingly common in children. In babies, it has been used with morphine to reduce cumulative exposure to morphine (20,27). For this indication the established route of administration is intravenous infusion.

In a study comparing 39 babies who received dexmedetomidine matched with 39 babies who did not, the total dose of opioids was lower in the group that received dexmedetomidine (median 1,155 mcg/kg vs 1,841 mcg/kg) (27). In another study (20), in 12 of 18 babies (66%), opioids were reduced within 24 hours of initiation of dexmedetomidine. Babies who received dexmedetomidine, compared with those on opioids only, had a significantly shorter duration of ventilation and 19 of 28 babies (68%) were extubated while receiving dexmedetomidine.

Effective doses of dexmedetomidine are extrapolated from older children (therapeutic window 0.4–0.8 mcg/L; optimum level 0.6 mcg/L; maximum 1mcg/L) (34) and used in preterm babies such as in small numbers in some centres in the USA and Canada (35). However, the clinical applicability and efficacy of these levels in reducing morphine exposure are not yet determined and more information on the side effect profiles is needed for precise estimate of the optimal levels and doses.

The dexmedetomidine doses selected for this study are 0.125, 0.25, and 0.5 mcg/kg/hr without a loading dose. These dosing regimens were informed by data from published literature primarily on

its off-label use in neonates, including two pharmacokinetic (PK) studies, one small randomised controlled trial, and 13 observational studies. Intravenous administration has been reported since 2009 and its use has progressively increased, including in extremely preterm, preterm, and term neonates. Overall, published reports describe exposure in more than 900 neonates, of whom approximately 30% were less than 32 weeks' postmenstrual age (please refer to Appendix 1 for previous doses used, treatment duration and reported adverse events for continuous intravenous dexmedetomidine in neonates).

Observational studies indicate that dexmedetomidine dosing in neonates is variable, with a range of regimens employed to achieve adequate pain control. This variability may reflect differences in metabolism or dose-response relationships, with real-world data documenting maximum infusion rates of up to 1.2 mcg/kg/hr. Therefore, as a risk minimisation strategy, this study incorporates a dose-titration design. Neonates randomised to the dexmedetomidine arms will commence at 0.125 or 0.25 mcg/kg/hr, respectively, with titration to the target dose (0.25 or 0.5 mcg/kg/hr) permitted only if the initial dose is well tolerated, and the predefined criteria for pain scores and adverse effects (outlined in Figure 1 - IMP infusion rate and morphine dose modifications) are met.

Across the published literature, dexmedetomidine has been well tolerated with no safety signals identified. Adverse effects reported to date are consistent with its adrenergic mechanism of action, most notably bradycardia and hypotension.

We will assess two different doses (the upper and lower ends of the accepted range), confirm adequate plasma levels, and determine whether dexmedetomidine, at either or both doses, is efficacious in reducing cumulative morphine dose. Dexmedetomidine doses will be fixed with no loading dose to avoid sudden haemodynamic changes on starting the infusion. The infusion will be given at half rate for the first 24 hours and then continue to follow the process outlined in Figure 1 so that the dexmedetomidine concentration rises gradually and - avoid sudden haemodynamic changes. Comparing two fixed dose levels rather simplifies the study interpretation, which has a primary endpoint of the (titratable) cumulative morphine dose. However, to ensure safety, some titration of the dexmedetomidine dose will be permitted if the baby shows signs or symptoms of haemodynamic instability.

Although there is high interindividual variability in morphine and dexmedetomidine clearance, randomisation cannot be stratified on drug clearance. We will measure pharmacokinetics in case potential confounding results from more high clearance participants, who therefore require higher doses for the same drug exposure. Pharmacokinetic and/or pharmacodynamic models will be developed from these data to confirm and/or better characterise the dose-concentration-effect relationship of each drug in the target population.

Participants will receive the Investigational Medicinal Product (IMP) (one of the two doses of dexmedetomidine or the placebo) infusion for 120 hours (5 days) from randomisation. This is an efficacy trial where internal study validity is paramount, and hence the restricted timespan. The median duration of ventilation in the target population is 4-days, but we know that some babies may be ventilated for much longer. Allowing the dexmedetomidine/placebo to continue indefinitely will be impractical as the costs of dexmedetomidine and matched placebo will be prohibitive. An unrestricted duration would also lead to a much larger standard deviation in the primary outcome of cumulative morphine dose and increase the required sample size. Demonstrating the efficacy of dexmedetomidine in reducing morphine over a 120-hour duration will provide sufficient evidence that it may improve clinically relevant short and longer-term outcomes.

1.2.4. Justification of the use of the experimental intervention and placebo comparator

Dexmedetomidine, when used an adjunct to opioids such as morphine could reduce the absolute amount of morphine used for analgesia in preterm babies (25,36,37) and lead to improvements in short and long-term outcomes with a reduced negative impact on the developing brain. Analgesia is increased or decreased according to pain scores based on subjective measurements of pain. To ensure that knowledge of the allocated regimen does not introduce bias, this will be a blinded, placebo-controlled trial. The control group will be babies randomised to receive morphine infusion with a masked placebo infusion at the same rate at which the intervention groups will receive dexmedetomidine infusion. The clinical team will then titrate the morphine dose in response to changes in the pain scores and other clinical indications without knowing whether the infant is receiving one of the two doses of dexmedetomidine or the placebo thus removing any bias.

2. Aims, Objectives and Outcome Measures

2.1. Aims

To investigate, in ventilated preterm babies, whether infusion of two different doses of dexmedetomidine (Intervention 1 – 120-hour infusion of dexmedetomidine (0.5microgram/kg/hour) or Intervention 2 – 120-hour infusion of dexmedetomidine 0.25microgram/kg/hour), given in addition to a standard dose of morphine, reduces cumulative exposure to morphine and its related short- and long-term adverse effects, when compared to a 120-hour infusion of placebo + morphine comparator, respectively.

2.2. Primary Objective and Outcome Measure

To determine, in ventilated preterm babies, if dexmedetomidine is efficacious in reducing the cumulative dose of morphine over 120 hours, from starting the dexmedetomidine or placebo infusion (Table 1).

2.2.1. Primary Objective

Table 1. Primary objective

Objective	**To determine, in ventilated preterm babies, if dexmedetomidine is efficacious in reducing the cumulative dose of morphine over 120 hours from starting the dexmedetomidine or placebo infusion**	
Outcome Measure	**Time Point**	**Method of collection**
Cumulative dose of morphine over 120 hours from starting the dexmedetomidine or placebo infusion	120 hours from start of infusion	Drugs and infusion charts

2.3. Secondary Objectives and Outcome Measures

Table 2. Secondary objectives

Secondary objective 1	**To investigate the potential benefits and safety of dexmedetomidine, given with morphine infusion on clinical outcomes in neonatal care**

Outcome Measure (safety outcomes are indicated by an asterisk*)	**Time Point**	**Method of Collection**
Pain (measured by standardised preterm pain scale)	120 hours from start of infusion	Standardised preterm pain scale – Neonatal Pain Agitation and Sedation Scale (N-PASS) – 2-hourly
Total duration of morphine infusion (hours)	120 hours from start of infusion	Drug and infusion charts
Use of additional morphine bolus	120 hours from start of infusion	Drug and infusion charts
Total additional morphine (microgram/kg and number of additional boluses)	120 hours from start of infusion	Drug and infusion charts
Total dose and duration of other analgesics	120 hours from start of infusion	Drug and infusion charts
Total duration of ventilation (hours)	Until first sustained extubation	Clinical notes
Number of episodes of bradycardia requiring intervention*	120 hours from start of infusion	Clinical notes
Number of episodes of desaturation (SaO_2 < 80% requiring intervention with oxygen or ventilatory changes)*	120 hours from start of infusion	Clinical notes
Heart rate (each hour)*	120 hours from start of infusion	Clinical notes
Oxygen saturation (each hour)*	120 hours from start of infusion	Clinical notes
Fractional inspired oxygen (each hour)*	120 hours from start of infusion	Clinical notes
Blood pressure (every two hours) *	120 hours from start of infusion	Clinical notes
Requirement of additional vasopressor support*	120 hours from start of infusion	Clinical notes
Time to reach at least 140 ml/kg/day full milk feeds (hours) after randomisation	At discharge	Feed charts
Evidence of preterm brain injury	At discharge	Cranial ultrasound or MRI scan reports

Bronchopulmonary dysplasia	At 36 weeks' PMA or discharge, whichever is earlier	Clinical notes
Length of intensive, high-dependency, and total neonatal care (days)	At discharge	Clinical notes
Late onset infection –microbiologically confirmed	At discharge	Clinical notes
Necrotising enterocolitis (Bell's Stage 2 or 3)	At discharge	Clinical notes
Retinopathy of prematurity	At discharge	Clinical notes
Death*	At discharge	Clinical notes
Parent experience	At discharge	Bespoke parent questionnaire

Secondary objective 2	**To determine whether there is an imbalance in dexmedetomidine or morphine exposure resulting from inter-individual variability in clearance**	
Outcome Measure	**Time Point**	**Method of Collection**
Dexmedetomidine and morphine cumulative Area Under the Curve (AUC)	3 days from start of infusion	Drug and infusion charts, concentrations of dexmedetomidine and morphine in plasma samples on the three days following the start of infusion

Secondary objective 3	**To determine, in ventilated preterm babies, if dexmedetomidine is efficacious in reducing the cumulative AUC of morphine over 120 hours from starting the dexmedetomidine or placebo infusions**	
Outcome Measure	**Time Point**	**Method of Collection**
Dexmedetomidine and morphine cumulative AUC	3 days from start of infusion	Drug and infusion charts, concentrations of dexmedetomidine and morphine in plasma samples on the three days following the start of infusion

Secondary objective 4	**To compare neurodevelopmental outcomes between groups at 2 years of age corrected for prematurity**

Outcome Measure	Time Point	Method of Collection
Survival without moderate or severe neurodevelopmental impairment at 2 years of age corrected for prematurity including visual, hearing, gross motor, cognitive and language impairments	2 years of age corrected for prematurity	Self-reported questionnaire using the PARCA-R and added motor, visual, and hearing assessment OR, if no response, routine 2-year clinical follow-up assessments obtained from clinical notes and as reported by the site investigator

Exploratory objective 1	**To quantify the relationship between dexmedetomidine concentration and haemodynamic markers (heart rate and blood pressure)**	
Outcome Measure	**Time Point**	**Method of Collection**
Dexmedetomidine and morphine cumulative AUC, heart rate and blood pressure	120 hours from start of infusion	Drug and infusion charts, concentrations of dexmedetomidine and morphine in plasma samples on the three days following the start of infusion

Exploratory objective 2	**To quantify the relationship between dexmedetomidine concentration and pain score**	
Outcome Measure	**Time Point**	**Method of Collection**
Dexmedetomidine and morphine cumulative AUC and pain scores	120 hours from start of infusion	Drug and infusion charts, concentrations of dexmedetomidine and morphine in plasma samples on the three days following the start of infusion

3. Trial Design and Setting

3.1. Trial Design

A three-arm, multicentre, blinded, randomised placebo-controlled, efficacy trial with a superiority hypothesis testing framework, a built-in safety run-in period and planned single interim analysis with integral Pharmacokinetic-Pharmacodynamic (PKPD) analysis.

Babies will receive dexmedetomidine (one of two infusion doses) or a matched placebo, in addition to a morphine infusion for 120 hours. Total cumulative dose of morphine and other outcomes will be measured at the end of the 120-hour infusion, at a postmenstrual age of 36 weeks or at discharge from the neonatal unit if sooner, and at 2 years of age corrected for prematurity.

Details on the internal pilot phase and progression criteria are given in Section 3.4.

3.2. Trial Setting

Babies will be identified and recruited from 15 UK Neonatal Intensive Care Units.

3.3. Type of Trial by Risk Category (for CTIMPS only)

Applying the MHRA scheme, on the basis of IMP marketing authorisation status, this trial is categorised as Type B (testing authorised medicinal products according to treatment regimens outside the marketing authorisation).

3.4. Internal pilot

An internal pilot phase has been built into the trial to allow a feasibility assessment of key metrics including recruitment and primary outcome data collection. The pilot phase assessment criteria (Table 3) will be used to determine the progression of the trial, 9 months after the first site opens (unless agreed otherwise with the funder).

Table 3: Internal pilot phase metrics used to evaluate trial feasibility

	Red **Consider stopping recruitment**	**Amber** **Initiate recovery plan**	**Green** **Continue recruitment**
Number of sites open	<9	9 to 14	≥15
Number of participants randomised	<46 (<70%)	46 to 64 (70% to <100%)	≥65 (≥100%)
Percentage of participants who received at least 48 hours of the trial infusion	<50%	50–74%	≥75%
Percentage of participants with primary outcome data available[1]	<60%	60–94%	≥95%
[1]for babies receiving at least 48 hours of trial infusion (primary analysis population)			

The Trial Steering Committee (TSC) will meet to assess trial progress against these criteria. The TSC will make a recommendation to the Trial Management Group (TMG) and funder about trial progression. The final decision on trial progression will be made by the funder.

4. Eligibility

4.1. Inclusion Criteria

- <32 weeks' gestational age at birth AND at least 160 hours from birth
- expected to require at least 48 hours of ventilation from randomisation
- receiving/requiring morphine infusion

4.2. Exclusion Criteria

- mother has received any opiates during pregnancy (excluding during labour)
- baby:
    - has major congenital anomaly

- is haemodynamically unstable despite receiving two or more inotropes
- is highly likely to be transferred to another hospital within 5 days of randomisation
- has no realistic prospect of survival (as judged by the clinical team)
- contraindicated to Dexmedetomidine as per the local SmPC
- history or evidence of any other medical condition that would expose the participants to an undue risk of a significant AE or interfere with study assessments during the course of the trial (as determined by the clinical judgment of the investigator)

4.3. Co-enrolment

As this is a controlled trial of an investigational medicinal product (CTIMP), babies who are participating in other CTIMPs cannot be enrolled and babies who participate will not be able to enrol in other CTIMPs.

Participation in non-interventional studies such as observational studies will be permitted. Co-enrolment in other trials where the intervention is not an IMP may be permitted. Such co-enrolments will be decided on a trial by trial basis, it will be discussed initially with the TMG before agreement is sought between the Chief Investigator of the two trials. If enrolling in any other type of research, the potential participant will be made aware of the trial timelines and visit schedule to ensure involvement is manageable, and not too demanding of their time.

4.4. Recruitment

Babies will become eligible when they are more than 160 hours from birth, require ventilation, are expected to remain ventilated for at least 48 hours and receive morphine. Babies will be recruited and randomised after parents give full written, informed consent. As many babies may need ventilation, and therefore become eligible unexpectedly, parents will be given information about the study in advance.

Clinicians will discuss potential participation with parents whose babies are likely to become eligible e.g., extremely premature babies who are likely to need mechanical ventilation during their neonatal care. In such cases, if the clinicians feel it is appropriate to do so and the parents agree, written informed consent may be obtained prior to the baby becoming eligible, and the baby can then be randomised if they become eligible.

4.5. Participant Identification

Potentially eligible babies will be identified and their parents approached by appropriately trained clinical staff at each recruiting site.

Babies who could potentially participate (<32 weeks' gestation at birth) who may require ventilation for at least 48 hours and morphine infusion for analgesia will be identified by the clinical team. As it can be difficult to approach parents at a time that is emotionally fraught, parents will be given information about the study in advance and may be screened and consented prior to their baby becoming eligible for the trial.

Parent(s) with parental responsibility will be approached in the antenatal period, at or around the time of the antenatal appointment. Parent(s) will be given study information and have an opportunity to discuss the study with a clinician or a member of the research team. However, consent for participation will only be taken after the baby is born and is <32 weeks' gestation at birth.

Publicity materials will be used to raise awareness of the trial to families. The trial will have a public facing website, social media pages and posters. Posters will be displayed around participating neonatal

units to inform parents about the trial. Posters will include QR codes linking to a short, animated video explaining the trial and how and when their baby may become eligible.

4.6. Screening

Parents of preterm babies (<32 weeks' gestation at birth) who may require ventilation for at least 48 hours and morphine infusion for analgesia will be approached by the clinical team. The clinical care team will review personal patient information to identify and screen potential babies for the trial.

5. Consent

Written informed consent for each baby will be sought from their parents prior to performing any trial related procedure.

Parents who are approached about their baby potentially joining the trial will be given the opportunity to ask questions throughout the whole process. Written consent will be taken by the Principal Investigator (PI) or their delegate (e.g., co-investigator, research nurse) as documented on the Site Delegation Log. It remains the responsibility of the PI to ensure informed consent is obtained appropriately and that those on the delegation log have been appropriately trained.

5.1. Postnatal Written Informed Consent Pathway

Some women may present in labour such that there is no opportunity or sufficient time to give information antenatally. Babies of such parent(s) will be given trial information after the baby is born.

Clinicians will discuss potential participation with parents whose babies are likely to become eligible e.g., babies born <32 weeks' gestational age. In such circumstances, as the time after birth can be extremely stressful for the family, parents will be given information about the trial as soon as deemed appropriate by the clinical team. If the clinicians feel it is appropriate to do so and the parents agree, written informed consent may be obtained prior to the baby becoming eligible and the baby can then be randomised if they become eligible for the trial. For babies that are no longer eligible, a reason (if given) for not randomising will be captured in the eCRF.

Some babies who are initially stable become unwell and require mechanical ventilation unexpectedly. If they are eligible, and parents have not been given the information previously, they will be given the information about the trial as soon as deemed appropriate by the clinical team and written informed consent can be obtained when parents have had the opportunity to ask questions. If the parent provides written informed consent, the baby can be randomised.

A Parent Information Sheet (PIS) will be provided to facilitate the informed consent process. The parent(s) will be given sufficient time to read the PIS and to discuss their participation with others as they wish (e.g., family members, or other healthcare professionals outside of the site research team). Investigators or their delegate(s) will ensure that they adequately explain the aim, trial treatment, anticipated benefits, and potential hazards of their baby taking part in the trial to all parents who are approached. Prior to taking consent, the Investigator or delegate should be satisfied that the responsible parent or parent(s) has a full understanding of the trial. It will be clearly conveyed that participation is voluntary, not wishing to participate will in no way impact the care that they or their baby receive and anyone who does consent may withdraw from the trial at any time.

The parent must give explicit consent for the regulatory authorities, members of the research team and representatives of the Sponsor to have direct access to the participant's (baby's) medical records.

The ICF will include consent to contact the parent via phone, letter, and/or email when the baby is 2 years of age corrected for prematurity to obtain information on later neurodevelopmental outcomes. This will take place after a wellbeing check has been carried out as described in section 8.2.6.

The original ICF will be stored in the Investigator Site File (ISF), a copy will be filed in the baby's medical notes, and a copy (or original where appropriate) retained by the parents.

Once the baby is entered into the trial, the baby's unique trial identification number will be entered on the ICF maintained in the ISF. In addition, a copy of the signed ICF will be uploaded to the trial database for the Nottingham Clinical Trials Unit (NCTU) to review as a part of central monitoring. Details of the informed consent discussions will be recorded in the baby's medical notes. This will include date of discussion, the name of the trial, version number of the PIS given to participant, version number of ICF signed and date consent received. Participation in the trial will also be clearly documented in each eligible baby's medical notes.

Throughout the trial the baby's parents will have the opportunity to ask questions about the trial. Any new information that may be relevant to baby's continued participation will be provided. Where new information becomes available which may affect parents' decision to continue, parents will be given time to consider and if happy to continue will be verbally re-consented. Re-consent will be documented in the medical notes. The parent's right to withdraw the baby from the trial will remain.

Electronic copies of the PIS and ICF will be available from the NCTU and will be printed or photocopied onto the headed paper of the local institution.

Details of all parents approached about their baby participating in the trial will be recorded on the Participant Screening/Enrolment Log.

6. Randomisation

Eligible babies born at <32 weeks' gestational age who are expected to be ventilated for at least 48 hours and who require or are receiving morphine will be enrolled and randomised, but only if all eligibility criteria are satisfied. Babies can be randomised at any time after they are 160 hours old, but IMP infusion should be started only after the baby is at least 168 hours (7 completed days) old.

Prior to enrolment of a participant (baby), trial eligibility must be confirmed by the investigator (or delegate) and informed consent must be provided and signed by the potential participant's parent and the investigator (or delegate). Baseline data will then be collected and recorded in the electronic Case Report Form (eCRF) and the participant enrolled using the online trial randomisation system.

Data will be collected for all participating babies until hospital discharge, and until 2 years of age corrected for prematurity. Contact details of consenting parents/legal guardian (postal address, email, phone number and favoured method of contact) will be collected prior to discharge and stored securely within the trial database for maintaining contact, and sending out questionnaires at 2 years of age corrected for prematurity. Parents will also have the option to give consent to retain this information to send them the trial newsletters, final results, and to make contact about participation in any related future studies. These will be optional and declining consent for these will not affect the baby's participation in the trial.

To maintain contact, families will be sent reminder text messages and first- and second-year birthday cards followed by a £20 voucher with the 2-year questionnaire. In addition, other study information, such as newsletters to update families on study progress, will also be sent to maintain engagement and promote data collection and longer-term follow-up of babies.

6.1. Randomisation and Allocation Concealment

The unit of randomisation is the individual baby. Randomisation will be provided by a secure online randomisation system hosted at the NCTU. Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the study (as detailed on the Site Delegation Log). The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance which sites will be made aware of in advance.

After the baby's eligibility has been confirmed and informed consent has been obtained, the participant can be randomised into the trial. The online randomisation system includes an eligibility checklist. The investigator must check all the eligibility criteria and confirm them on the online system. All questions and data items on the eligibility checklist must be answered. If data items are missing, the system will not allow randomisation, but it can be resumed once the information is available.

Following randomisation, a confirmatory email will be sent to the randomising clinician, local PI, the named research nurse, and the local pharmacy containing a specific IMP pack code ensuring blinding is maintained. A blinded randomisation notification will be sent to the Chief Investigator and the NCTU. This will contain the information provided in the eligibility checklist and the randomisation in a printable format. It must be printed and added to the participant's medical records.

Participants will be randomised individually in a 1:1:1 allocation ratio to one of:

- 120-hour infusions of dexmedetomidine (0.5mcg/kg/hour) + morphine,
- 120-hour infusions of dexmedetomidine (0.25mcg/kg/hour) + morphine, or
- 120-hour infusions of matched placebo + morphine.

A probabilistic minimisation algorithm will be used to ensure balance across the randomised groups across the following factors:

- recruiting site
- gestational age at birth
- sex
- postnatal age
- previous morphine exposure (after birth)

Full details of the randomisation specification will be stored in a confidential document at NCTU.

Following interim analysis, if recruitment to one of the active doses of dexmedetomidine arms is stopped, randomisation will continue using a 1:1 allocation ratio to either:

- the remaining dexmedetomidine arm + morphine, or
- matched placebo + morphine.

6.2. Blinding

To maintain blinding of allocation, dexmedetomidine and placebo ampoules provided for the trial will be identical in appearance and packaged in blinded participant kits. 44 provides an overview of the blinding status of all individuals involved in the management and delivery of the trial.

Table 4. Blinding status of individuals involved in the trial

Trial role	Blinding status	Comments
Participants and their parents	Blinded	

All site personnel	Blinded	
Chief Investigator	Blinded	The CI will remain blinded to treatment allocation overall, except in their role as medical monitor, should there be a SUSAR
Trial Management Team	Blinded	
Data Management Team	Blinded	
Database System Developers	Unblinded	The database system developers are unblinded, as they are responsible for the pack management system and the allocation of the IMP stock.
Trial Statisticians	Blinded	The trial and senior trial statisticians will not have access to treatment allocations or data which have the potential to unblind them until after the database lock for the analysis
Independent statistician	Unblinded	A statistician, independent of the trial team, will be responsible for the generation of confidential reports for the Data Monitoring Committee (DMC), interim analysis and other potentially unblinding data, and will therefore be unblinded to treatment allocation
Those responsible for analysing drug concentration data	Unblinded	Individuals analysing drug concentration data during the trial will not participate in Trial Management Meetings
Independent DMC	Unblinded	Review unblinded data

6.3. Unblinding Procedure

For DEXTA, unblinding of each baby will not occur routinely, to protect the integrity of the long-term follow-up. Although the clinical care team and the parents will be unaware of treatment allocation, they may stop the study infusion (without withdrawing the baby from the trial) if there are significant concerns about adverse effects. For example, if the baby has a significant increase in the number or severity of episodes of bradycardia or intractable (i.e. not responding to usual treatment) hypotension as determined by the attending clinician. This will be done without unblinding.

Unblinding prior to the end of the trial may occur if the participant experiences a medical emergency or Suspected Unexpected Serious Adverse Reaction (SUSAR) related to the trial intervention, but only if deemed necessary for ongoing clinical care. The PI and the baby's attending neonatal consultant will discuss this with the trial team (including the CI) and unblinding will occur following NCTU procedures.

6.4. Emergency Unblinding

This process will only be used to unblind the participant allocation during the emergency, where knowledge of DEXTA treatment is essential for further clinical management. To protect the safety and

well-being of participants during a medical emergency, unblinding will be performed within the REDCap trial database by site staff who have been delegated the responsibility.

In the event of an emergency unblinding occurring, the NCTU and CI will be notified automatically by email that an allocation has been unblinded but will not be made aware of the participant's allocation. NCTU will notify the Sponsor as soon as possible. The NCTU will then send the Emergency Unblinding Form to the site research team for completion. Once returned this should be reviewed by the Trial Manager /Senior Trial Manager, PI, CI and Sponsor and the completed form filed in the ISF and Trial Master File (TMF).

The decision to continue treatment for baby's whose allocation has been revealed will be decided by the baby's clinical care team. The baby will remain in the trial unless their parent(s) choose to withdraw them.

6.5. Unblinding for SUSAR

The process for unblinding for a SUSAR will be the same as for emergency unblinding. To ensure medical oversight the Chief investigator and/or Deputy Medical Expert will be unblinded as necessary.

7. Trial treatments / interventions

7.1. Treatment

7.1.1. Name and Description of Investigational Medicinal Product

Table 5. Description of the Investigational Medicinal Product

Drug	DexmedeTOMIDine*	Placebo (0.9% sodium chloride)
IMP or NIMP	IMP	IMP
Description of active substance	Chemical origin	Chemical origin
Pharmaceutical form	Solution for infusion	Solution for injection/infusion
Concentration	Contains 100 micrograms of dexmedeTOMIDine in 1ml	Contains 0 micrograms of dexmedeTOMIDine in 1ml
Unit size	2ml glass ampoule	2ml glass ampoule
Excipients	Sodium chloride Water for injections	Water for injections
Appearance	Clear colourless solution	Clear colourless solution
Manufacturer	Product with UK or EU marketing authorisation	Sharp Clinical Services (UK) Limited
Labelling	Commercial label removed and labelled in compliance with UK regulatory requirement	In compliance with UK regulatory requirement
Packaging	Packaged in secondary containers	Packaged in secondary containers

Sourcing	Provided centrally from the sponsor via Sharp Clinical Services (UK) Limited	Provided centrally from the sponsor via Sharp Clinical Services (UK) Limited
IMP=investigational medicinal product; NIMP=non-investigational medicinal product *DexmedeTOMIDine will be written with upper case "TOMID" to reduce the risk of mix up with "Dexamethasone." Both drugs are typically shortened to "Dex". As dexamethasone is frequently used in neonatal practice, neonatal clinicians are used to referring to dexamethasone as "Dex". Trial sites will be trained and encouraged to use the full name for DexmedeTOMIDine or "Dexmed" in short.		

Each participant kit will be labelled with a unique kit number. This unique kit number will be assigned to a participant via **Error! Reference source not found.**6 and encodes the appropriate IMP to be dispensed in accordance with the treatment assignment for the participant.

Table 6. Description of Investigational Medicinal Product Participant Kit

Treatment group	**How supplied (blinded)** **Each pair of ampoules consisting of:**	**Participant kit presentation**
DexmedeTOMIDine 0.25 micrograms/kg/hr	Each pair of ampoules consist of: 1 x DexmedeTOMIDine 100 micrograms/ml ampoule 1 x Placebo ampoule	Each kit contains 7 pairs of ampoules
DexmedeTOMIDine 0.5 micrograms/kg/hr	2 x DexmedeTOMIDine 100 micrograms/ml ampoule	Each kit contains 7 pairs of ampoules
Placebo comparator	2 x Placebo ampoule	Each kit contains 7 pairs of ampoules

7.1.2. Regulatory Status of Drug

The regulatory status of each IMP is detailed in Table 5.

7.1.3. Product Characteristics

The product characteristics of each IMP are detailed in Table 5.

7.1.4. Drug Storage and Supply

The investigator, or an authorised designee (e.g., pharmacist) will ensure that all IMPs are stored in a secured area under recommended storage conditions, with access limited to the investigator and authorised personnel. The IMPs are for clinical trial use only and are to be used only within the context of this protocol.

All IMPs must be stored either in pharmacy or on the neonatal unit to enable participant recruitment at any time of day. The IMPs must be stored below 25°C and must be protected from light. Each trial

site is responsible for ensuring that temperature monitoring of the storage area is conducted in accordance with local policies and standard clinical practice.

Further information is detailed in the IMP manual.

7.1.5. Preparation and Labelling of Investigational Medicinal Product

IMP will be packaged and labelled according to Good Manufacturing Practice (GMP) guidelines and applicable UK regulations in secondary containers as individual participant kits as described in Table 7.

The preparation and administration of IMP is summarised in **Error! Reference source not found.**7. Further information is detailed in the IMP manual.

Table 7. Preparation and administration of Investigational Medicinal Product

Treatment group	**DexmedeTOMIDine 0.25 micrograms/kg/hr**	**DexmedeTOMIDine 0.5 micrograms/kg/hr**	**Placebo comparator**
Route of administration	Intravenous infusion	Intravenous infusion	Intravenous infusion
Dose preparation	One pair of ampoules (labelled A and B) will be used to prepare each infusion syringe. For participants < 800 grams, each infusion syringe is prepared by diluting: - 0.25 ml from ampoule A - 0.25 ml from ampoule B - 49.5 ml of diluent For participants ≥ 800 grams, each infusion syringe is prepared by diluting: - 0.5 ml from ampoule A - 0.5 ml from ampoule B - 49 ml of diluent A new infusion syringe must be prepared every 24 hours.		
Rate of infusion	Body weight adjusted infusion rate - Further information is detailed in the IMP manual. **For the first 24 hours, all participants will receive IMP at half the target infusion rate. Thereafter, the clinical team will monitor the pain scores using the N-PASS every 2–4 hours and the IMP infusion rate can be adjusted as per Figure 1 as needed.** **The working weight recorded at the start of the infusion will be used throughout the 120 hours of infusion.**		
Duration of treatment	Up to a maximum of 120 hours.		

7.1.6. Dosing Schedules

All participants will receive IMP as a continuous intravenous infusion for a maximum of 120 hours.

7.1.7. Dose Modifications

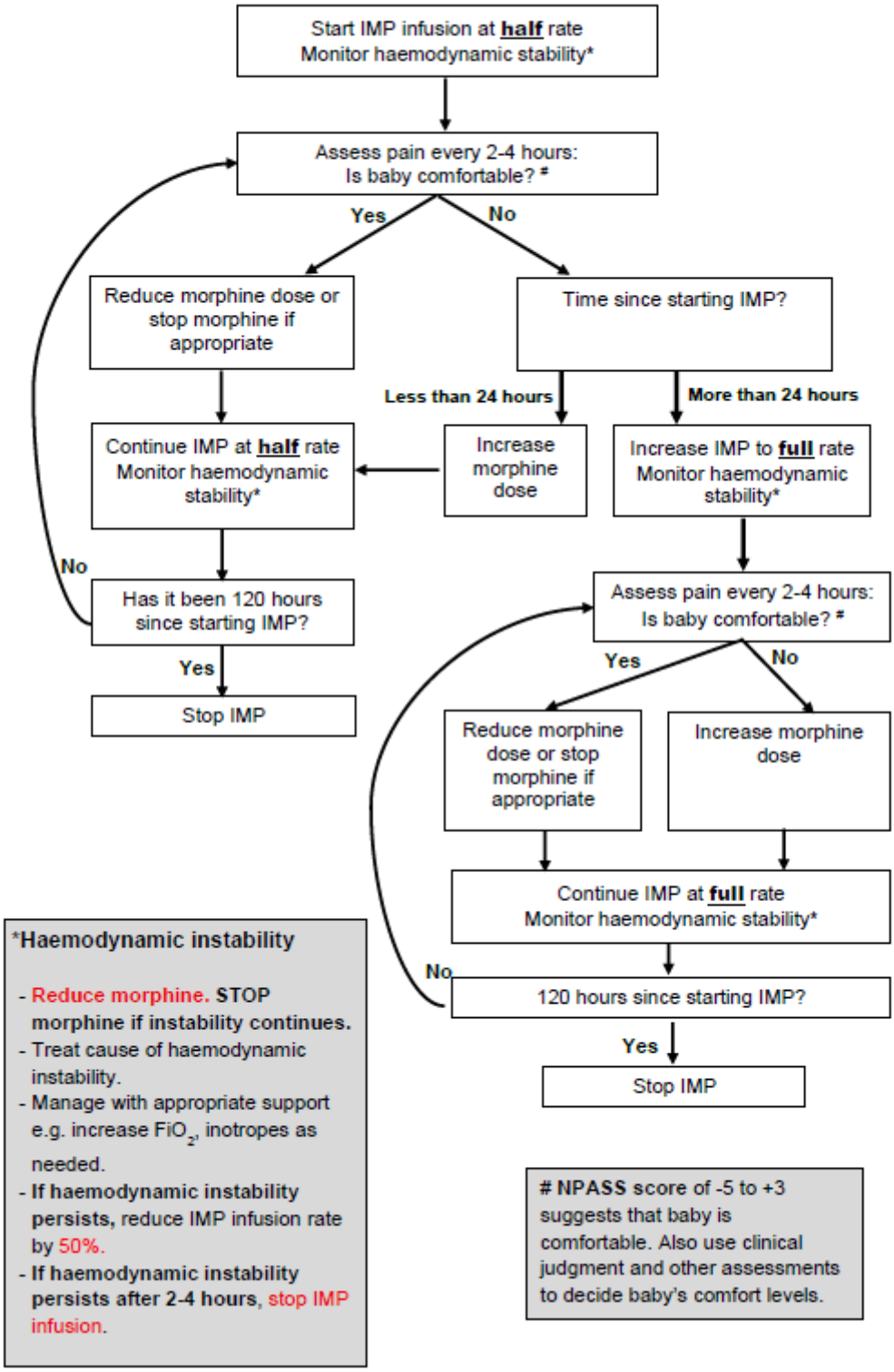


Figure 1. IMP infusion rate and morphine dose modifications

IMP infusion will be started at half the target infusion rate. The clinical team will assess for baby's pain and comfort level using the N-PASS and other clinical assessments (as in routine practice) every 2-4 hours for the 120-hour duration of the IMP infusion. N-PASS scores of -5 to +3 signify that the baby is comfortable (neither too sedated nor in pain). N-PASS score of >3 signifies baby is in pain.

If the baby is comfortable, morphine dose should be reduced. If further pain scores show that the baby is comfortable, morphine should be stopped. If the baby remains comfortable, IMP will be continued at the same infusion rate.

In the first 24 hours after starting the IMP, if the pain scores (or other clinical assessments) suggest that baby is in pain, morphine dose should be increased.

At or after 24 hours of starting the IMP infusion, if the pain scores (or other clinical assessments) suggest that baby is in pain, IMP infusion will be increased to the full rate.

After the increase in IMP infusion to full rate, if the pain scores (or other clinical assessments) suggest that baby is in pain, morphine dose should be increased.

After the increase in IMP infusion to full rate, if the pain scores (or other clinical assessments) suggest that baby is comfortable

- if the baby is still on morphine, morphine dose should be reduced, and morphine should be stopped if the baby remains comfortable.
- IMP infusion will be continued at the same rate.

At 120 hours from the start of the IMP infusion, the IMP infusion will be stopped. If the baby still needs analgesia, morphine or other analgesics should be given as per routine clinical practice.

At any point during the IMP infusion, if the baby has signs/symptoms of haemodynamic instability (such as bradycardia, hypotension, or desaturations)

- Reduce the morphine infusion. Morphine infusion should be stopped if haemodynamic instability persists.
- Treat the cause of the haemodynamic instability.
- Ensure optimal supportive management is provided e.g., increased oxygen, inotropes as needed.
- If haemodynamic instability persists, reduce IMP infusion by half.
- If haemodynamic instability persists 4 hours after reducing the IMP infusion to half, stop the IMP infusion.

The investigator may discontinue IMP administration at any time during the study, if the clinical care team and the investigator determine that discontinuation of the IMP is in the participant's best interest. The primary reason for IMP discontinuation should be recorded in the case report form.

7.1.8. Known Drug Interactions and other Therapies

Co-administration of dexmedeTOMIDine with anaesthetics, sedatives, and opioids could lead to an enhancement of effects, including sedative, anaesthetic and cardiorespiratory effects. In addition, the possibility of enhanced hypotensive and bradycardic effects should be considered in participants receiving other medicinal products causing these effects. Vital signs will be monitored throughout the study and is part of the safety monitoring of this study. If a baby is very well sedated or over-sedated according to the N-PASS and clinical examination, the morphine infusion should be weaned to obtain the desired level of analgesia and sedation. where severe, bradycardia or hypotension are concerns, clinical team should first consider reducing and subsequently stopping the morphine infusion as these are known side effects of opiates.

Dexmedetomidine will only be provided for the trial period. Sites may wish to consider providing it from their own sources after the study period although increasing the morphine rate as needed after discontinuing the trial infusion is another alternative. Clonidine is a similar drug (with a lower receptor affinity) that could be used instead.

Open-label alpha2-agonists use including dexmedetomidine or clonidine will be forbidden during the 120-hour IMP infusion because of the risk of overdose in the dexmedetomidine group. Babies who are on clonidine or similar drugs or have had these earlier in their care may be entered into the trial, but the clonidine or similar drug must be stopped for the duration of the 120-hour IMP infusion.

7.1.9. Concomitant Medications

All babies will receive supportive neonatal care as determined by the investigator according to institutional practices and baby's characteristics. Supportive care measurements will be recorded in the eCRF.

7.1.10. Trial Restrictions

Not applicable.

7.1.11. Assessment of compliance with Treatment

Babies will receive IMP from the investigator or designee, under medical supervision at the study site. The date and time of each IMP administration on the ward will be documented in the source documents and in the eCRF. IMP preparation and administration will be confirmed by two study site staff. Further information is detailed in the IMP manual.

7.1.12. Name and description of each Non-IMP

Not applicable.

8. Trial procedures and assessments

8.1. Summary of assessments

This is given in Table 8.

Table 8. Summary of assessments

	Enrolment	Randomisation	Post-randomisation						Follow-up
Timepoint	**-t_1**	**0**	**Day1***	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**36 weeks' PMA or discharge**	**2 years of age corrected for prematurity**
ENROLMENT									
Eligibility Screen	X								
Written informed consent	X								
Randomisation		X							
INTERVENTION									
120-hour infusions of dexmedetomidine (0.5microgram/kg/hour) plus morphine			X	X	X	X	X		
120-hour infusions of dexmedetomidine (0.25microgram/kg/hour) plus morphine			X	X	X	X	X		
120-hour infusions of placebo plus morphine			X	X	X	X	X		
ASSESSMENTS DURING 120-HOUR OF IMP INFUSION									
Neonatal Pain Agitation and Sedation Scale (N-PASS)[§]			X	X	X	X	X		
Total duration of morphine infusion			X	X	X	X	X		
Total additional morphine			X	X	X	X	X		
Total dose and duration of any other analgesics			X	X	X	X	X		
Total duration of ventilation			X	X	X	X	X		

Episodes of bradycardia requiring intervention			X	X	X	X	X		
Heart rate (hourly)			X	X	X	X	X		
Oxygen saturation (hourly)			X	X	X	X	X		
FiO_2 (hourly)			X	X	X	X	X		
Blood pressure (2 hourly)			X	X	X	X	X		
Need for vasopressor support			X	X	X	X	X		
Pharmacokinetic blood samples for 120 babies *				X	X	X			
ASSESSMENTS AT DISCHARGE									
Time to full milk feeds								X	
Brain injury								X	
Bronchopulmonary dysplasia (36 weeks PMA)								X	
Length of intensive, high-dependency, and total neonatal care (days)								X	
Parent experience								X	
Late onset infections – microbiologically confirmed								X	
Necrotising enterocolitis – Bells Stage 2 or 3								X	
Retinopathy of prematurity – Stage 2 or worse								X	
ASSESSMENTS AT 2 YEARS OF AGE CORRECTED FOR PREMATURITY									
Parent questionnaire (motor, visual, and hearing impairment)									X
PARCA-R (cognitive and language impairment)									X

*The Investigational Medicinal Product (IMP) infusion will start once the baby is 168 hours from birth. Day 1 will be the day that the IMP infusion starts. Samples for the pharmacokinetic studies will be taken on Days 2, 3 and 4 i.e., on 3 consecutive days following the day on which the IMP infusion was started. The samples will be taken while the participant is having blood sampling for routine clinical care.
[§]N-PASS scores will be recorded at least every 2 hours and additional scores will be recorded when the baby has any painful procedure e.g., heel prick, suction of the endotracheal tube.

8.2. Schedule of Assessments

The following assessments will be performed at each time point indicated in Table 8.

8.2.1. Baby born at <32 weeks' gestational age who may need to be ventilated for at least 48 hours and given morphine infusion

- Give information about the trial including PIS
- Obtain written informed consent

8.2.2. Baby born at <32 weeks' gestational age, >160 hours from birth, who is being ventilated or is going to be ventilated for at least 48 hours and given morphine infusion

- Give information about the trial including PIS
- Obtain written informed consent
- Randomise baby into the trial
- Collect of baseline data

8.2.3. Post-randomisation: IMP infusion

- When baby is 168 hours (7 completed days) old, start and give IMP infusion for 120 hours.

In all arms, IMP will be infused at half the target infusion rate for the first 24 hours and continue to follow the process outlined in Figure 1.

8.2.4. During the 120-hour IMP infusion

- Pain and sedation score using the Neonatal Pain Agitation and Sedation Scale (N-PASS) every 2-4hours and at the time of at any painful intervention e.g., heel prick, suction of endotracheal tube.
- Total dose and duration of morphine infusion in hours.
- Number and dose of additional morphine bolus (in microgram/kg and number of additional boluses) given.
- Name and dose of any other analgesic given (in microgram/kg and number of doses or hours of any infusion).
- Duration of mechanical ventilation (in hours) until the time of the first sustained extubation (baby extubated and remained off for at least 24 hours).
- Heart rate recorded every hour.
- Oxygen saturation every hour
- FiO_2 every hour
- Systolic, diastolic, and mean blood pressure recorded every 2 hours.
- Number of episodes of bradycardia that required clinical intervention
- Name and dose of any inotropes given (in mg/kg or microgram/kg and duration of infusion).
- 0.3–0.5 ml of blood sample on days 2, 3 and 4 of IMP infusion taken at the same time as blood sampling done for clinical care and stored to be sent to Analytical Services International (ASI) at St George's, University of London to analyse morphine and dexmedetomidine area under the concentration time curve – see section 8.4. The exact time and date that the sample was taken must be recorded and reported.

8.2.5. At discharge from neonatal care

- Any evidence of any preterm brain injury

- The time for the baby to reach at least 140 ml/kg/day full milk feeds in hours from the start of the infusion
- Bronchopulmonary dysplasia at 36 weeks' PMA or discharge, whichever is earlier
- Length of intensive, high-dependency, and total neonatal care in days
- Death
- Parent experience using a bespoke parent questionnaire
- *Late onset infections – microbiologically confirmed
- *Necrotising enterocolitis – Bells Stage 2 or 3
- *Retinopathy of prematurity – Stage 2 or worse

*These outcomes are included as they are included in the neonatal core outcome set (38).

8.2.6. At 2 years of age corrected for prematurity

At 2 years (i.e., prior to any planned contact from NCTU), site staff will check their hospital records for any record of infant death and any instances where the infant is no longer in the care of the biological mother. Contact information for the mother will be updated at these time-points where necessary. Any infant deaths will be reported to the NCTU within 24 hours of becoming aware of the event (see section 9.1) and will be recorded in the appropriate section of the CRF.

If a site reports that the infant is no longer in the care of the biological mother, NCTU will not distribute a follow-up questionnaire or birthday card to the mother. In such cases, the clinical team at site will be responsible for contacting the new carer(s) to obtain verbal consent for the NCTU send the questionnaire or birthday card. For infants where the clinical team are unable to make contact with the new carer(s) or the new carer(s) are unwilling to receive a follow-up questionnaire, data will be obtained from routine data sources where possible.

The 2-year questionnaire will collect the following:

- moderate or severe visual impairment (reduced vision uncorrected with aids, blindness in one eye with good vision in the other, or blindness or light perception only).
- moderate or severe hearing impairment (hearing loss corrected with aids, some hearing loss uncorrected by aids, or deafness).
- moderate or severe gross motor impairment (inability to walk or sit independently).
- moderate or severe cognitive impairment (PARCA-R non-verbal cognition scale standard score < -2 standard deviations; score < 70).
- moderate or severe language impairment (PARCA-R language development scale standard score < -2 standard deviations; score < 70).

8.3. Trial Procedures

8.3.1. Screening

Minimal screening data for babies entering the trial will be collected by each site and recorded within the trial database.

8.3.2. Informed consent

Informed consent will be obtained as described in Section 5.

8.3.3. Baseline Data Collection

After informed consent and eligibility assessments are complete, baseline data will be collected. Randomisation can be performed when the eligibility checklist is completed, and other baseline data

can be collected post-randomisation. These will include participant demographic data and clinical details of the baby's medical condition and care prior to randomisation. The full list of baseline data is listed in the Data Management Plan (DMP).

8.3.4. Eligibility Assessments

Babies who require mechanical ventilation and are expected to remain ventilated for at least 48 hours and receive morphine after randomisation will be assessed for eligibility. Parents will be approached in advance, or as soon as suitable, and introduced to the trial. If interested, parents will be provided with the trial PIS and asked to sign the written ICF. Following full written, informed consent, the baby will be assessed and if eligible, eligibility checklist will be completed. Eligibility will be confirmed and signed off by the PI (or their delegate) on the online randomisation system as described in Section 6.1.

For those babies who do not meet eligibility criteria, the parents will be informed of the reason explained and reassured that this will not impact the care of their baby.

8.3.5. Randomisation

Babies can be randomised at any time after they are 160 hours old. Randomisation will be performed by a suitably delegated member of the recruiting site research team as described in Section 6. As the trial intervention is blinded, neither the baby's parents nor the recruiting site staff will know which of the treatments the participant has been allocated to receive.

8.3.6. IMP Dispensing

The IMP can be prescribed as per the site's local guidelines. An IMP pack code, assigned to the correct treatment arm will be linked to the participant at the point of randomisation to allow the recruiting site to dispense the allocated IMP.

Following randomisation, IMP infusion should be started only after the baby is at least 168 hours (7 completed days) old, for all arms, infusion rate will start at half the rate and continue to follow the process outlined in Figure 1. The changes in infusion rate will be done by the nurses in the clinical care team.

8.3.7. Post Randomisation: Data Collection over 120-hour IMP Infusion

While on infusion, information will be collected over 120 hours from starting the dexmedetomidine or placebo infusion. It will be recorded from the paper or electronic drug and infusion charts and clinical records used in clinical care via electronic case report forms and questionnaires.

The total morphine dose received in this period will be recorded in detail – infusion dose and rate recorded every hour, any change in infusion rates and the dose and time of all additional boluses of morphine dose. These will be recorded from the start of the IMP infusion to the end of the 120 hours IMP infusion period which is the primary endpoint of data collection.

Additional data that need to be collected are listed in Section 8.2.4.

8.3.8. Day 2, 3 and 4 Pharmacokinetics Blood Samples

Blood samples (0.3 ml for babies <700g, 0.5 ml for babies ≥700g) for pharmacokinetics will be taken on days 2, 3 and 4 of the IMP infusion for 120 babies. The IMP infusion will start as soon as feasible after randomisation and once the baby is at least 168 hours old. Day 1 will be the day that the IMP infusion starts. Samples for the pharmacokinetic studies will be taken on days 2,3 and 4 i.e., on 3 consecutive days following the day on which the IMP infusion was started. The samples will be taken while the baby is having blood sampling for routine clinical care. These samples will be stored locally

and sent, in batches, to the Analytical Services International (ASI) Ltd at St George's - University of London as described in Section 8.4.

8.3.9. Data Collection at Discharge from Neonatal Care

Data that needs to be collected at this point are listed in Section 8.2.5 and will be collected from the paper or electronic clinical notes and parent questionnaires.

The time to reach full milk feeds will be the time from the start of the infusion to when the baby is receiving at least 140 ml/kg/day for 3 consecutive days.

Bronchopulmonary dysplasia will be defined, as in the National Neonatal Audit Programme 2024 guide to audit measures (15), by the level of respiratory support received at 36 weeks' postmenstrual age. When a baby is discharged from neonatal care before reaching 36 weeks' postmenstrual age, data from the time of discharge will be used. Respiratory support will be defined as receiving any of the following at the specific time: ventilation, non-invasive respiratory support including continuous positive airway pressure or high flow nasal cannula oxygen or oxygen treatment.

Evidence of brain injury will include:

- Grades 3 or 4 intraventricular haemorrhage (IVH)
- Post-haemorrhagic ventricular dilatation (PHVD)
- Cystic periventricular leukomalacia (PVL)

Length of intensive, high-dependency, and total neonatal care from the day of randomisation to the day of final discharge from neonatal care will be recorded from the baby's paper or electronic clinical records. If the baby is transferred from one neonatal unit to another, these will include days spent in all neonatal units that cared for the baby.

8.3.10. Follow-up at 2 Years of Age Corrected for Prematurity

Parent will be sent a £20 shopping voucher with a questionnaire to complete (either postal or online, via a text or email link, as per their preference) after a wellbeing check, using routine hospital records has been carried out. This will include the following measures to classify the main long-term outcome of survival without moderate or severe neurodevelopmental impairment at 2 years of age corrected for prematurity including visual, hearing, gross motor, cognitive and language impairment:

- Parent Report of Children's Abilities-Revised (PARCA-R)[32] to assess children's cognitive and language development
- Parent completed questionnaire items to assess children's vision, hearing and gross motor function

If the questionnaire is not returned despite text reminders, parents will be contacted by telephone and given the option to complete the questionnaire over the phone.

If for any reason parent questionnaires are not returned and parents cannot be contacted, data from routine clinical assessments will be obtained to collect the information as reported by the site investigator.

8.3.11. Transfers of babies

Data will be collected for all participating babies until discharge from neonatal care. For babies who are transferred to another hospital (known as the 'continuing care site') after completion of 120 hours of IMP infusion, a transfer pack will be provided with information on trial participation and instructions for data collection and completion.

Babies who are likely to be transferred within 120 hours (5 days) of starting the IMP infusion will be excluded (see Section 4.2). Despite this, if a participating baby is transferred within the 120 hours of IMP infusion, the intervention will be discontinued and data collection will be completed by the continuing care site.

The PI from the original recruiting site will be responsible for informing the trial co-ordinating site of the transfer and ensuring data collection is completed at the continuing care site. This will be facilitated by documentation about the trial that will be sent at the time of transfer identifying the continuing care site that the baby is participating in the trial.

8.4. Collection, Storage and Analysis of Clinical Samples for Pharmacokinetic Analyses

The only extra blood samples required for the trial will be for pharmacokinetic analysis, which will be collected with blood samples taken for routine clinical purposes.

The start of the drug infusions is designated day 1, and the PK samples should be taken on days 2, 3 and 4 at no set time points but whenever blood sampling is performed as part of clinical care. **The time, to the nearest minute, that the pharmacokinetic sample was drawn must be recorded. The time, to the nearest minute, when the IMP infusion was started and the time at which the IMP infusion was increased to full rate must also be recorded accurately.** Start, stop and infusion rates of IMP, any interruptions in IMP and morphine infusions must also be recorded.

Samples can be drawn from either heel pricks, indwelling arterial, or central venous catheters, or by vein puncture or when performed on clinical indications.

Simultaneous measurement of dexmedetomidine, morphine, morphine-3-glucuronide and morphine-6-glucuronide will be undertaken from plasma extracted from each PK blood sample.

8.4.1. Specimen Preparation, Handling, Storage and Shipping

Pharmacokinetics blood samples: 0.3–0.5 ml, whole blood per sample will be drawn into a supplied potassium EDTA tubes (K2 EDTA, purple cap). Sites will be given detailed instructions on preparing, handling, storage, and shipping.

In brief, the sample should be gently inverted in the EDTA tube 6–10 times to ensure the anticoagulant is evenly distributed throughout the sample. The sample should then be sent to have plasma extracted by centrifuging at 3,500 rpm at room temperature for 15 minutes either in a designated sample processing area or at the neonatal unit or local biochemistry laboratory. Plasma should then be removed and transferred to amber tubes (propylene screw-cap tubes) and frozen at -80^{o}C. It is important not to overfill the tubes – such that some headspace is available for expansion during freezing.

Sample labels will be provided, and it is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the General Data Protection Regulation (GDPR). Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

The samples will then be transported on dry ice by courier to Analytical Services International (ASI), St George's – University of London. Samples will be checked against the sample list/manifest on arrival at the laboratory and assigned a unique ASI laboratory number, which is used by ASI to identify the sample thereafter throughout the analytical processing.

All study samples will be retained at ASI for 6 months following the completion of the final report of the study and will then be destroyed according to ASI local procedures.

8.4.2. Sub Studies

No sub studies are planned.

8.5. Withdrawal and Discontinuation Procedures

8.5.1. Withdrawal Prior To Randomisation

Any parents that request to withdraw their consent **prior to randomisation** will not be randomised or included in the trial.

8.5.2. Discontinuation and Withdrawal Post Randomisation

Parents may, at any stage, withdraw their consent for any trial-related activities including follow-up and/or receiving trial-related communications (Table 9). The NCTU must be informed of all requests by parents to stop their baby's involvement in the trial. Appropriate action will be taken to ensure that the parent's wishes are followed. Sites will be trained to determine which activities participants may wish to withdraw from and they will be encouraged to continue to provide access to their data without pressurising them.

Table 9. Post-randomisation Discontinuation and Withdrawal

Withdrawal type	Withdrawal procedure	Use of data
Discontinuation of the intervention due to parental choice	Parents that request to stop treatment, will be asked to continue to complete questionnaires and complete the outcomes. Information on reason for stopping trial treatment will be recorded by the site if given and will not affect ongoing care. These babies will be marked as stopped treatment on the trial database.	Data collected prior to or after discontinuation of the intervention will be retained and used in the analysis.
Discontinuation of the intervention by investigator/clinical team	Investigator/clinical team that requests to discontinue the trial treatment if the baby has a significant adverse event due to dexmedetomidine will be asked to continue to collect data and complete the outcomes. Parents of such babies will be asked to complete questionnaires.	Data collected prior to or after discontinuation of the intervention will be retained and used in the analysis.

	These babies will be marked as stopped treatment in the trial database.	
Withdrawal from the trial due to parental choice	Parents (baby) that request to withdraw from the trial, will be asked to continue to complete questionnaires and complete the outcomes. Information on the reason for withdrawal will be recorded by the site if given and will not affect ongoing care. These babies will be marked as withdrawn on the trial database.	If parents agree for further data collection and have questionnaires sent to them, these data will also be collected and retained. If parents decline further data collection, data collected prior to withdrawal will be retained and used in the analysis.
Withdrawal from follow up questionnaires due to parental choice	Parents that request to discontinue from trial questionnaires will be marked as withdrawn from questionnaire collection on the trial database and no further contact relating to questionnaires will be made.	Data collected prior to participant withdrawal will be retained and used in the analysis.
Withdrawal from long-term follow-up as per parental choice	Parents that request to discontinue from trial questionnaires will be marked as withdrawn from long-term follow up questionnaire collection on the trial database and no further contact relating to the 2-year corrected age questionnaires will be made.	Data collected prior to participant withdrawal will be retained and used in the analysis.
Complete withdrawal from the trial as per parental choice	Parents that request to fully withdraw from the trial will be marked as complete withdrawal on the trial database. Information on reason for complete withdrawal will be recorded by the site if given and will not affect ongoing care. No further contact relating to the trial will be made.	Data collected prior to participant withdrawal will be retained and used in the analysis but all participant contact information will be redacted (marked with xxs) and no further contact will be made.

8.6. Post Trial Intervention Care

Usual clinical care will continue after completion of the 120 hours of the IMP infusion following randomisation. No further trial related intervention will be done. Further care will be as per local neonatal unit protocols and decisions of the clinical care team.

Treatments given after completion of the 120 hours of IMP infusion following randomisation and/or any treatment outside of the trial will not be funded by the trial sponsor. Babies with a continuing need for analgesia may need ongoing pain relief for which morphine or other analgesics, as per routine practice, may be used.

Data collection will continue until discharge from neonatal care.

Parents may be sent trial newsletters (if they consent to receiving them), and babies will be sent first and second year birthday cards. Parents will be sent the questionnaire to complete follow up at 2 years of age corrected for prematurity. A well-being check will be performed using hospital records prior to sending the birthday cards and the questionnaire. Parents will be given a £20 unconditional voucher with this questionnaire.

9. Adverse Event Reporting

9.1. Reporting Requirements

Table 10. Definitions for Adverse Event Reporting

Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant being administered a medicinal product and which does not necessarily have a causal relationship with this treatment. **Comment:** An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an IMP, whether or not related to the IMP.
Adverse Reaction (AR)	All untoward and unintended responses to an IMP related to any dose administered. **Comment:** An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that: • Results in death • Is life threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Or is otherwise considered medically significant by the Investigator** **Comments:** The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on participants/event outcome or action criteria.

	* Life threatening in the definition of an SAE refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. ** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.
Serious Adverse Reaction (SAR)	An Adverse Reaction which also meets the definition of a Serious Adverse Event
Unexpected Adverse Reaction (UAR)	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

IMP, investigational medicinal product

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 (and subsequent amendments). The Investigator will assess the seriousness and causality (relatedness) of all AEs experienced by the participant with reference to the Reference Safety Information Dexamedetomidine-EVER-Pharma-SmPC-July-2023, section 4.8. This should be documented in the source data.

9.2. Adverse Events and Reporting Requirements/Procedures

All medical occurrences, which meet the definition of an AE and **occur during the 120-hour IMP infusion and in the 72 hours after the IMP infusion** has been discontinued should be recorded in the source data. Of these, only selected AEs experienced during treatment will be reported via the CRFs.

The safety profile of morphine in the trial population is well established. As such we will not report on the side effects of morphine.

Known side effects of dexmedetomidine that are deemed appropriate for the trial population (see table 11) will be recorded directly within the eCRF as targeted Adverse Events. Side effects will be reportable from the start of infusion until 72 hours after the infusion has ceased. Should any of these events meet the criteria for an SAE, they will also be reported as a SAE.

The severity of adverse events will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) classification. Severity classification for each adverse event will be reported primarily by the site Principal Investigator, with subsequent review by blinded trial clinicians.

Table 11. Known side effects of dexmedetomidine that will be recorded as targeted AEs.

Event	Description/criteria
Hyperglycaemia	Hyperglycaemia needing starting insulin treatment or increasing ongoing insulin infusion or a reduction in glucose intake
Hypoglycaemia	A glucose level of <2.6 mmol/L or needing increased glucose provision e.g., a glucose bolos or increase in infusion rate.
Metabolic acidosis	pH<7.10 with increased base excess < -15 mmol/L
Myocardial ischaemia or infarction	Diagnosed on a clinically indicated ECG or ECHO
Atrioventricular block	Diagnosed on a clinical indicated ECG
Cardiac output decreased	Diagnosed on a clinical indicated ECG
Cardiac arrest	Needing cardiopulmonary resuscitation
Hyperthermia	Any temperature recording of >39^{o}C
Hypotension*	Requiring additional vasopressor support
Bradycardia*	Requiring clinical intervention

*to be reported as secondary outcomes

9.2.1. Serious Adverse Events and Reporting Requirements/Procedures

Investigators will report AEs that meet the definition of an SAE.

AEs defined as serious, and which require expedited reporting as an SAE, should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE.

Causality of an event will be categorised as one of the following:

- Definitely related
- Probably related
- Possibly related
- Unlikely to be related
- Unrelated

On becoming aware that a participant has experienced an SAE, the Investigator (or delegate) must complete the electronic SAE form within the REDCap database. The form should be completed as soon as possible and no later than 24 hours after first becoming aware of the event. The site investigator will define the causality of the SAE and sign the form electronically.

Completion of the electronic SAE form will generate a unique SAE reference number and will trigger an alert, via email, to NCTU. The SAE reference number will be quoted on all correspondence regarding the SAE. NCTU will request Medical Monitor assessment via the REDCap database.

In the unlikely event that the electronic SAE reporting system is unavailable, a paper SAE form must be completed by the site investigator (or delegate). For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments.

Paper SAE forms (only in the unlikely event that the electronic SAE reporting system is unavailable) must be emailed to NCTU-SAE@nottingham.ac.uk as soon as possible and no later than 24 hours after becoming aware of the event. NCTU will request Medical Monitor assessment via email.

9.2.2. Sites

For SAE Forms completed by someone other than the PI, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The original form should be retained at site in the Site File and a copy returned to the NCTU.

Investigators must also report SAEs to their own Trust in accordance with local practice.

9.2.3. NCTU

On receipt of an SAE form (either electronic or paper), seriousness and causality will be reviewed independently by the Medical Monitor (Chief Investigator or delegate) responsible for determining causality assessments. An SAE judged by the Investigator to have a reasonable* causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Chief Investigator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the current version of the Reference Safety Information (RSI)) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR). Any events classified as a SUSAR will trigger an immediate alert to the NCTU Quality Assurance team and to the trial Sponsor office.

*reasonable equates to possible, probable or definitely related in the opinion of either the Investigator or Chief Investigator

9.2.4. Provision of Follow-up Information

Participants will be followed up until resolution or stabilisation of the event or until discharge from neonatal care whichever comes first. Follow-up information will be provided on a new SAE Form.

9.2.5. Events that do not require expedited reporting

Episodes of desaturations, bradycardia, and/or hypotension requiring vasopressor support: Preterm babies have frequent episodes of desaturations and bradycardia. Hypotension can occur due to prematurity and related co-morbidities such as late onset infections. These events are also known adverse effects of dexmedetomidine infusion. They are also recognised side effects of morphine infusion and if such events occur, the clinical team should consider a reduction in the infusion rate of morphine first.

9.2.6. Events that do not require reporting on a Serious Adverse Event Form

The following are regarded as expected SAEs for the purpose of trial and should not be reported on an SAE form. These events should be reported on the eCRF at 36 weeks' PMA or discharge from neonatal care (whichever is later).

Known complications of prematurity and of dexmedetomidine and morphine: Any event that is deemed by the investigator to be a known complication should not be reported as an SAE and should be recorded in the baby's medical records, as per usual practice. Complications listed as trial outcomes (Table 2) will be reported as outcomes and do not need reporting as SAEs.

9.2.7. Monitoring Pregnancies for potential Serious Adverse Events

Not applicable.

9.3. Reporting Period

All AEs should be recorded in the medical notes from the commencement of treatment allocation until 72 hours after the end of the 120-hours of IMP infusion. For babies transferred to another hospital during their participation in the trial, the randomising hospital retails all responsibility for the collection of data from the receiving hospital and the ongoing reporting of AEs.

9.4. Reporting to the Competent Authority and Research Ethics Committee

9.4.1. Suspected Unexpected Serious Adverse Reactions

The NCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

9.4.2. Serious Adverse Reactions

The NCTU will report details of all SAEs and SARs (including SUSARs) to the MHRA and REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

9.4.3. Adverse Events

Details of all AEs will be reported to the MHRA on request.

9.4.4. Other safety issues identified during the trial

The MHRA and REC will be notified immediately if a significant safety issue is identified during the trial.

9.5. Reporting to Investigators

Details of all SUSARs and any other safety issue which arises during the trial will be reported to PI. A copy of any such correspondence should be filed in the Investigator Site File.

9.6. Reporting to Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

9.7. Reporting to Third Parties

No reporting of adverse events to third parties is expected. Any safety issues identified during the trial will be notified to the MHRA.

9.8. Safety run-in period procedures

The purpose of this pre-planned safety run-in phase is to allow early review of safety processes. The run-in will recruit a minimum of two participants into each active treatment group.

A minimum of two participants per active treatment arm has been selected in line with precedent from similar studies, where small numbers were sufficient to demonstrate the absence of any immediate, unexpected safety concerns. This sample size is not intended to provide formal statistical power but is considered adequate to fulfil the objective of the safety stage, namely to ensure that early safety signals can be monitored prior to progression into the main phase of the trial. The proposed sample size has been approved by the DMC.

Each run-in participant will be observed closely for pre-specified safety outcomes from the time of the first IMP infusion until 72 hours post infusion – this represents the critical window for acute safety concerns. This observation period will normally occur while the baby remains in hospital. However, if discharged (either home or to another hospital) occurs before 72 hours), daily clinical checks and direct communication will be arranged to ensure safety data are captured.

The DMC will review run-in safety data once at least two participants in each active treatment group have completed the post-infusion 72-hour observation period. The DMC will then issue a formal recommendation to the TSC, who will make a decision against the charter.

Stopping rules (the occurrence of one of the following):

- One fatal AE that is considered related to IMP
- Any two serious adverse events considered related to IMP (independent of within or not within the same system-organ-class)
- If more than two patients develop a ≥ Grade 3 Common Terminology Criteria for Adverse Events (CTCAE) toxicity within the same system-organ-class
- If the incidence or severity of AEs indicate a potential health hazard to patients treated with the study treatment

If the trial is suspended due to safety concerns or as a result of the predefined stopping rules, it may only be resumed following approval of a substantial amendment by the regulatory authority.

10. Data Handling and Record Keeping

10.1. Source Data

To allow for the accurate reconstruction of the trial and clinical management of the participant, source data will be accessible and maintained.

Source data will be kept as part of the participant's medical notes generated and maintained at sites. Each site will record the location of source data at their site using a source data location log prior to commencing recruitment. Data that are not routinely collected elsewhere may be entered directly onto the eCRF; in such instances the eCRF will act as source data and this will be clearly defined in the source data location log and recorded.

For this trial, source data refers to, though is not limited to, the participant's medical notes, MRI and ultrasound data, laboratory results for tests recorded, data recorded directly into the eCRF, and Parent reported follow-up data (follow-up questionnaires).

All data collected directly from participants will be considered as source data within the eCRF. Where paper questionnaires are issued to participants these will be returned to the NCTU for data entry and

will be considered source data. Where questionnaire data is obtained via telephone, this data will be entered directly into the eCRF by a member of the NCTU and will be considered source data.

10.2. CRF Completion

Data for the trial will be captured directly into a REDCap eCRF. Data reported on each eCRF will be consistent with the source data and any discrepancies will be explained. Staff delegated to complete eCRFs will be trained to adhere to ICH-Good Clinical Practice (GCP) guidelines and trial-specific guidance on the completion of the eCRF.

In all cases it remains the responsibility of the site PI to ensure that the eCRF has been completed correctly and that the data are accurate. Where applicable for the trial this will be evidenced by the signature of the site PI on the eCRF.

10.3. Data Management

Details about data handling will be specified in the Data Management Plan (DMP). This will include the agreed validation specification which will validate data for consistency and integrity as it is entered.

All trial data will be entered into a REDCap database with participants identified only by their unique trial number and initials. The database will be developed and maintained by NCTU. Access to the database will be restricted and secure (password protected) and eCRFs will be restricted to those personnel approved by the CI or local PI and recorded on the trial delegation log. Any missing or ambiguous data will be queried with the site via the eCRF in REDCap using the data quality tool. Sites should respond to the data queries in a timely manner, ideally within 2 weeks of the query being raised. All access and data transactions will be logged in a full audit trail.

Contact details will be logged separately to the trial CRF data, to ensure participant identifiable data is separate to data used for analysis.

Participant's eCRF data will be reviewed on an ongoing basis once they are deemed to have a complete set of data that has passed data validation checks (i.e. there are no data queries outstanding). Once all participant data has been received and reviewed and the statistical plan has been finalised, the trial database will be hard-locked (set to read only and access removed). This will be done prior to analysis. It is planned that there will be 2 database locks after discharge and 2-year follow-up.

Paper questionnaires returned to NCTU will be entered by a member of NCTU and a sample will be reviewed by a separate member of the NCTU. Further details will be documented in the current version of the DMP. Data obtained from participant reported outcomes will not be subject to data queries. Decisions on how to treat anomalous data will be made by members of the TMG blinded to allocations and documented on a trial decision log.

10.4. Archiving

In compliance with the ICH/GCP guidelines and applicable regulations, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the trial. These will be retained for at least 15 years or for longer if required. If the responsible investigator is no longer able to maintain the trial records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the CI on behalf of the sponsor shall be finally archived securely in the Microsoft cloud which has multiple redundant systems and backup services. This archive shall include all trial databases and associated meta-data encryption codes. Access to files

once archived (e.g. for inspection purposes), will be managed by the NCTU archivist and will only be accepted on approval of the sponsor.

10.5. Data Sharing

Individual participant medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol.

Parents contact details, including name, address, telephone/mobile number and email will be shared between NCTU and third parties (where required) for the purposes of issuing questionnaires and electronic reminders (text/email) for the trial.

Any personal data will be held in a secure database using encryption, with restricted password protected access. Only appropriate members of the participating site team and NCTU research team will have access to these data.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in computer files.

Data generated as a result of this trial will be available for inspection on request by University Hospitals of Derby and Burton Foundation Trust, NCTU, the REC, local R&D departments and the regulatory authorities.

De-identified individual participant data may be shared with researchers external to the trial research team in accordance with the NCTU data sharing procedure. All requests for data should be sent to the Nottingham Clinical Trials Unit.

11. Quality control and quality assurance

11.1. Site Set-up and Initiation

All participating PIs will be asked to sign the necessary agreements and supply a current curriculum vitae (CV) to NCTU. The CV should be signed within the last 2 years. All members of the site research team will also be required to sign a site delegation and training log. Prior to commencing recruitment all sites will undergo a process of initiation and will have completed any necessary training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documents, instructions, and other documentation required for the conduct and reconstruction of the trial. NCTU must be informed immediately of any change in the site research team.

11.2. Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. NCTU will be in regular contact with the site research team to check on progress and address any queries that they may have. The trial team will check incoming eCRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Additional on-site monitoring visits may be triggered, for example by poor eCRF return, poor data quality, lower than expected SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required, NCTU will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow NCTU trial staff access to source documents as requested.

11.3. Audit and Inspection

The PI will permit trial-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The PI will comply with these visits and any required follow up. Sites are also requested to notify NCTU of any MHRA inspections.

The TMF and evidence of audits will be made available upon request for regulatory inspections.

11.4. Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and its amendments) the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a "serious breach" is a breach which is likely to effect to a significant degree the safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial. Sites are therefore requested to notify NCTU of any suspected trial-related serious breach of GCP and/or the trial protocol. Where NCTU is investigating whether a serious breach has occurred sites are also requested to cooperate with NCTU in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action. Serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment could potentially meet the criteria of a Serious Breach and sites may be suspended from further recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group and the Trial Steering Committee, the REC and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

12. End of Trial Definition

The end of trial will be the final database lock. This will allow sufficient time for the completion of protocol procedures, data collection and data input. NCTU will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Where the trial has terminated early, NCTU will inform the MHRA and REC within 15 days of the end of trial. NCTU will provide them with a summary of the clinical trial report within 12 months of the end of trial.

13. Statistical Considerations

13.1. Determination of Sample Size

In support of the sample size calculations, we audited the cumulative dose of morphine over 120-hours at three hospitals. Of 23 babies who received morphine for at least 48 hours, the median cumulative dose was 1.44mg/kg (interquartile range (IQR) 0.72 to 1.88mg/kg; minimum 0.44 to maximum 4.42mg/kg). We anticipate that the distribution of the cumulative dose will be right-skewed and propose a log-transformation of data for analysis, with the treatment effect therefore expressed as a ratio of two geometric means.

In order to progress ultimately to a larger definitive pragmatic trial, we are looking for evidence of a strong signal of a reduction in cumulative morphine dose, given that a second drug, dexmedetomidine, is being given in addition to morphine. Therefore, we have designed the trial to detect a 30% reduction in the geometric mean cumulative dose of morphine in 120 hours.

Two observational studies in newborn babies comparing a dexmedetomidine group with a 'no dexmedetomidine' group have observed large reductions in additional opioid requirements. Sellas et

al., (27) reported a 37% reduction in median cumulative dose of morphine in a retrospective cohort study of 39 babies receiving dexmedetomidine after invasive surgery, compared to 39 matched controls. O'Mara et al., did not report the cumulative dose, but found that the mean duration of treatment was significantly shorter: an average of 12.5 days in the dexmedetomidine group as compared to 20 days in the opioid group (20). Both these studies suggest that a large reduction in morphine requirement is a reasonable expectation with the addition of dexmedetomidine.

The sample size for the trial is based on two related primary comparisons (each dose of dexmedetomidine vs placebo comparator, respectively). It includes a planned single interim analysis to allow one or both doses of dexmedetomidine to be stopped for futility (i.e., no observed reduction in cumulative dose of morphine when compared to the placebo comparator) and controlling the family-wise error rate at 5% (one-sided).

Assuming a standard deviation of log transformed cumulative dose of 0.6 (observed in the audit data), a maximum of 60 randomised babies per group are needed to detect a 30% reduction in the geometric mean cumulative dose of morphine over 120 hours (i.e., a ratio of geometric means of 0.7) between a dexmedetomidine group and the placebo comparator group, with 90% marginal power under the least favourable configuration of a 10% reduction in the other dexmedetomidine group using a generalised Dunnett testing procedure (39). The interim analysis will be conducted at half of the planned maximum sample size (50% information fraction). Details on stopping boundaries are described in section 13.3.4.

12 shows the probability of making correct and incorrect decisions at the end of the trial about whether dexmedetomidine reduces the cumulative dose of morphine over 120 hours using this design (based on 1,000,000 simulations).

Table 12. Probability of making correct and incorrect decisions regarding efficacy at the planned end of the trial

Scenario	Probability of declaring at least one dose effective	Probability of declaring dose with largest effect is effective	Expected sample size of trial
Both doses effective[1]	97.1%	90.8%	179
One dose effective[1] and the other has no effect	90.9%	90.9%	164
Both doses have no effect	5.0%	2.8%	140

[1] i.e., a 30% reduction in geometric mean cumulative dose of morphine over 120 hours

The primary analysis population will include babies who receive at least 48 hours of trial infusion. Data from the National Neonatal Research Database suggest that about 55% of preterm babies who are ventilated, remain ventilated for at least 48 hours (3). Babies will be randomised after the clinical decision to ventilate and give morphine infusion for pain relief, if the clinician thinks that the baby is likely to need these for at least 48 hours. However, the clinician's prediction may be inaccurate. Babies may come off the ventilator sooner than expected if the respiratory condition improves rapidly e.g., drainage of air leaks, or treatment of underlying condition such as infections. Since the clinical team will be blinded to trial allocation and all other clinical care will be standard, we expect this proportion to be similar in the three trial arms.

To ensure that the study is adequately powered despite the premature discontinuation of trial drug in some randomised participants, we have inflated the sample size to 120 at the interim analysis (~40 per group) with a maximum sample size of 240 randomised babies, if both doses continue to the end of the trial (a maximum of 80 per group). This inflation will also account for those babies where the primary outcome data will not be available, e.g., if the baby dies within 120 hours after starting the treatment, or parents decide to withdraw their baby following randomisation (expected to be <5%).

Since the clinical team will be blinded to trial allocation and all other clinical care will be standard, we expect a similar proportion of babies to have missing primary outcome data across all arms. We will recruit from Neonatal Intensive Care Units and participants are unlikely to be transferred or discharged before collection of the primary outcome data. We therefore expect minimal loss to follow up.

The independent Data Monitoring Committee will, in addition to their typical duties, monitor the sample size assumptions regarding the standard deviation and sample size inflation against the accumulating data during the trial.

13.2. Definitions of Outcome Measures

13.2.1. Primary Outcome Measure

The primary outcome will be the **cumulative dose of morphine over 120-hours from starting the dexmedetomidine or placebo infusion** measured as the sum of the total dose of morphine (in microgram/kg) required, including the loading dose (if used), dose infused, and additional boluses given over the 120 hours infusion of the IMP (dexmedetomidine or placebo).

13.2.2. Secondary outcome measures

Outcome measure (safety outcomes indicated by an asterisk*)	Description
Over 120 hours from start of infusion	
Pain	Assessed by the Neonatal Pain Agitation and Sedation (N-PASS) every 2 hours and at the time of any painful intervention such as heel prick, suction of the endotracheal tube. This score will be summarised as the percentage of time the baby is comfortable (N-PASS score between -5 and 3 inclusive) i.e. baby neither too sedated nor in pain
Total duration of morphine infusion	In hours from when the IMP (dexmedetomidine or placebo) infusion starts to end of the 120-hour IMP infusion
Use of additional morphine bolus	Whether the baby was given any additional morphine as bolus

Outcome measure (safety outcomes indicated by an asterisk*)	Description
Total additional morphine given as additional boluses (microgram/kg)	The sum of all additional (bolus) doses given over the 120 hours IMP (dexmedetomidine or placebo) infusion for babies who receive additional morphine
Total number of additional boluses of morphine	Number of additional boluses per baby who received additional boluses over the 120 hours IMP (dexmedetomidine or placebo) infusion
Total dose and duration of other analgesics	Number and percentage of babies who needed additional analgesics will be summarised along with the following for each additional analgesic: total dose (in mg/kg or microgram/kg, as appropriate), number of doses (count), and duration of infusion (in hours) of other analgesics. These will include but not be limited to paracetamol, other opioids such as fentanyl, and benzodiazepines
Total duration of ventilation (hours)	Hours from the start of infusion to the first sustained extubation (i.e., the baby comes off the mechanical ventilator and remains off for at least 24 hours)
Episodes of bradycardia requiring intervention*	Count of the number of episodes of bradycardia where the baby's heart rate was below 100 beats per minute and the attending clinician intervened such as provided stimulation, increased ventilatory support or inspired oxygen, or gave positive pressure ventilation to help the baby's heart rate to recover
Number of episodes of desaturation (SaO_2 < 80% requiring intervention with oxygen or ventilatory changes)*	Count of the number of episodes of desaturation where the saturation level (SaO2) dropped below 80% and the attending clinician intervened with oxygen or ventilatory changes to increase the oxygen in the blood stream.
Heart rate each hour*	In beats per minute
Blood pressure every two hours *	Systolic, diastolic and mean arterial pressure in mm of Hg
Oxygen saturation each hour*	In percentage

Outcome measure (safety outcomes indicated by an asterisk*)	Description
FiO_2 each hour*	In percentage
Requirement of additional vasopressor support*	Number and percentage of babies who required additional vasopressor support will be summarised along with the following: - Number (count) and total volume (in ml/kg) of any additional fluid, such as normal saline, blood transfusion given to provide vasopressor support - Dose (in mg/kg or microgram/kg, as appropriate) and duration of infusion (in hours) of any additional inotropes such as dopamine, dobutamine, adrenaline, noradrenaline, given to provide vasopressor support
Morphine and dexmedetomidine Area Under the Concentration Time Curve	AUC(0-∞) for each drug will be derived from population pharmacokinetic models based on the drug concentrations, dose histories, and covariates: body weight, postmenstrual and postnatal age. AUC(0-∞) will be derived from individual clearance estimated from the population pharmacokinetic model. Published population pharmacokinetic models (Anand et al, 2008, Potts et al, 2009) will be used to provide individual clearance estimates.
At discharge from neonatal care	
Time to reach at least 140 ml/kg/day full milk feeds (hours) after randomisation	From start of infusion to when the baby is receiving at least 140 ml/kg/day sustained for 3 consecutive days for babies who were not receiving full milk at the start of the infusion (i.e., yet to reach full milk feeds since birth or feeds reduced or withheld due to ventilation)
Evidence of preterm brain injury	Ascertained from any cranial ultrasound scan or MRI scan reports performed as part of routine clinical care including: - Grades 3 or 4 intraventricular haemorrhage - Post haemorrhagic ventricular dilatation - Cystic periventricular leukomalacia
Bronchopulmonary dysplasia (BPD) (at 36 weeks' postmenstrual age or	BPD defined as per National Neonatal Audit Programme 2024 definition as receiving any of the following respiratory support at 36 weeks postmenstrual age: - ventilation or

Outcome measure (safety outcomes indicated by an asterisk*)	Description
discharge from neonatal care, whichever is earlier)	- non-invasive respiratory support including continuous positive airway pressure - high flow nasal cannula oxygen or - oxygen treatment
Length of neonatal care (days)	From start of infusion to discharge from neonatal care. Total number of days of neonatal care will be calculated as well as number of days in each of: - Neonatal Intensive Care* - Neonatal High Dependency Care* - Neonatal Special Care* *defined as in the NHS Neonatal Critical Care Service Specifications 2024 (or equivalent for sites in Scotland) For babies that are transferred from the recruiting neonatal unit, days spent in all neonatal units that cared for the baby will be included.
Late onset infection – microbiologically confirmed	Defined as blood or cerebrospinal fluid culture positive of a pathogenic organism taken after 72 hours of age as per the National Neonatal Audit Programme 2024 measure
Necrotising enterocolitis (NEC) -Bells Stage 2 or 3	Bells Stage 2 or 3 NEC as determined by clinical features, radiological signs, surgical findings, or histopathology or postmortem results
Retinopathy of prematurity (ROP) - Stage 2 or worse	Determined as per the results of routine ROP screening
Death*	Ascertained from routine hospital records
Parent experience	Measured by a bespoke parent questionnaire - can be collected from the end of the treatment period up until discharge. In any cases where discharge has occurred but these data haven't been collected, then site staff can phone the parent and enter the data on REDCap.
At 2 years of age corrected for prematurity	

Outcome measure (safety outcomes indicated by an asterisk*)	Description
Survival without moderate or severe neurodevelopmental impairment at 2 years of age corrected for prematurity	Survival to two years of age corrected for prematurity will be ascertained from routine hospital records. Moderate or severe neurodevelopmental impairment at 2 years of age corrected for prematurity will be defined as presence of one or more of: • moderate or severe visual impairment (reduced vision uncorrected with aids, blindness in one eye with good vision in the other, or blindness or light perception only) • moderate or severe hearing impairment (hearing loss corrected with aids, some hearing loss uncorrected by aids, or deafness) • moderate or severe gross motor impairment (inability to walk or sit independently) • moderate or severe cognitive impairment (PARCA-R non-verbal cognition scale standard score < -2 standard deviations; score < 70) • moderate or severe language impairment (PARCA-R language development scale standard score < -2 standard deviations; score < 70)

13.3. Analysis of Outcome Measures

Analysis and reporting of the trial will be in accordance with CONSORT extensions for multi-arm trials and adaptive designs (40,41). All analyses will be specified in the Statistical Analysis Plan (SAP) and finalised prior to the interim analysis.

The main analysis population for primary and secondary outcomes will be randomised babies who received at least 48 hours of trial infusion with analysis according to randomised allocation.

The safety analysis population will be randomised babies who received at least one dose of trial infusion with analysis according to randomised allocation.

13.3.1. Analysis of Primary Outcome

The primary analysis population will comprise babies who receive at least 48 hours of trial infusion with data available on cumulative dose of morphine over 120-hours from starting the dexmedetomidine or placebo infusion, regardless of discontinuation of the trial infusion and/or the morphine infusion between 48 and 120 hours. Babies who die within 120 hours from starting the infusion will not be included in the primary analysis population. Although a small number of deaths are expected in this period, these are expected to be similar across all trial arms.

The primary comparative analysis will use a mixed effects linear regression model to compare log-transformed cumulative morphine dose between groups (each dexmedetomidine dose versus placebo comparator, respectively) adjusting for gestational age and if technically possible, the other minimisation factors with site as a random effect. A random effect for 'pregnancy' will be nested within site, to account for the correlation between outcomes for infants born from a multiple pregnancy. The between-group treatment effect will be presented as the ratio of geometric means with corresponding confidence interval for the two primary comparisons (each dexmedetomidine dose versus placebo comparator).

It is anticipated that the primary outcome will be collected for nearly all babies who receive at least 48 hours of trial infusion, but if appropriate, sensitivity analyses will be conducted to determine the robustness of the results, by imputing missing primary outcome data. An additional analysis will include all babies randomised with primary outcome data collected, regardless of the length of the trial infusion.

13.3.2. Analysis of Secondary Clinical Outcomes

Secondary outcomes will be considered as supportive of the primary outcome and will be summarised and analysed for the main analysis population (unless otherwise specified). Between-group comparisons of secondary outcomes will use appropriate statistical regression models (depending on the outcome data type), using a generalised linear mixed model framework, again with adjustment for minimisation factors as described for the primary outcome. Secondary outcomes for blood pressure, heart rate, oxygen saturation and FiO_2 over time in each group will be presented descriptively in graphs (safety analysis population only). Secondary outcomes for parent experience and from the neonatal core outcome set will also be summarised using descriptive statistics only.

In addition, serious adverse events and secondary outcomes marked as safety outcomes will be summarised descriptively for the safety analysis population.

13.3.3. Analysis of Secondary Pharmacokinetic Outcomes

Pharmacokinetic outcomes will be estimated using the observed dose histories of dexmedetomidine and morphine along with measured concentrations of each drug to fit nonlinear mixed effects pharmacokinetic models of each drug. For each drug, individual predictions of the primary pharmacokinetic parameters clearance and volume of distribution will be generated for each participant. These will be used to derive the cumulative area under the concentration time curve from time 0 to the end of IMP dosing (AUC(0-t)) and the total AUC(0-∞).

To ensure drug handling is balanced across groups, log transformed clearance, the parameter which determines AUC(0-∞), of both dexmedetomidine and morphine will be presented as the ratio of geometric means with corresponding confidence interval for each dexmedetomidine dose versus placebo comparator.

To investigate differences in morphine exposure between groups, log transformed AUC(0-t) and AUC(0-∞) will be derived for morphine, morphine-3-glucuronide and morphine-6-glucuronide and compared across arms. The between-group treatment effect will be presented as the ratio of geometric means with 95% confidence interval for each primary comparison (each dexmedetomidine dose versus placebo comparator).

In an exploratory pharmacokinetic/pharmacodynamic modelling analysis, dexmedetomidine and morphine concentration with time will be modelled along with pain and sedation scores, assuming

either a continuous or ordered categorical scale. Linear and Hill equations will be tested to derive concentration effect relationships of each drug with pain and sedation.

13.3.4. Planned Interim Analysis

A single interim analysis will be conducted to potentially allow one or both doses of dexmedetomidine to be stopped for futility once (i) 120 babies have been randomised (half of the planned maximum sample size), and (ii) data collection on their cumulative dose of morphine over 120 hours from starting the infusion is completed.

Results of the interim analysis will be presented to the independent members of the DMC in order for them to make a recommendation to the Trial Steering Committee (TSC). The DMC should consider recommending that recruitment into one or both experimental intervention groups (i.e., doses of dexmedetomidine) be stopped if there is no observed reduction in cumulative dose of morphine when compared to the placebo comparator (i.e., ratio of geometric means > 1). The TSC will consider the recommendation from the DMC and report their decision to the Trial Management Group (TMG), sponsor and funder. The trial has not been designed to allow for early stopping for efficacy at the interim analysis, so there is no efficacy stopping boundary.

In the eventuality that the trial continues for at least one dose, the final observed test statistic(s) will be evaluated against the lower stopping boundary of -1.91 (p-value < 0.028).

13.3.5. Planned Final Analyses

Analysis and reporting of the trial findings will take place at two distinct stages:

1. After all data collection for primary and secondary outcomes up to discharge from neonatal care has been completed
2. After completion of follow-up at 2 years of age corrected for prematurity

13.3.6. Planned Subgroup Analyses

An exploratory subgroup analysis will be conducted to assess the consistency of the treatment effects for the primary outcome across the gestational age range, sex, and prior morphine exposure using the statistical test of interaction. This may help inform the interpretation of the findings, but also the future trial of clinical and cost effectiveness.

14. Trial Organisational Structure

The roles and responsibilities for each organisation are documented in the Contractual Agreement and the responsibilities of the (Sponsor/CI/NCTU) specifically are detailed in the Delegation of Responsibilities.

14.1. Sponsor

The University Hospitals of Derby and Burton NHS Foundation Trust is the sponsor of the DEXTA trial. The role and responsibilities of the Sponsor are outlined in the trial Delegation of Responsibilities (DoR).

14.2. Clinical Trials Unit

The trial is co-ordinated by the Nottingham Clinical Trials Unit (NCTU). The role and responsibilities of the Trials Unit are outlined in the DoR.

14.3. Trial Management Group (TMG)

The TMG will include those individuals responsible for the day-to-day management of the trial, such as the CI, Statistician, Trial Manager, Data Manager, with other members of the trial team attending as required. The role of the group is to (i) ensure high quality trial conduct to time and within budget, (ii) to monitor all aspects of the conduct and progress of the trial, (iii) ensure that the protocol is adhered to, and (iv) take appropriate action to safeguard participants and the quality of the trial itself. The TMG will report to the Independent TSC.

14.4. Trial Steering Committee (TSC)

The role of the TSC is to maintain oversight of the trial. The TSC should include members who are independent of the Investigators, their employing organisations, funders and Sponsors. The TSC should monitor trial progress and conduct. The TSC will consider and act, as appropriate, upon the recommendations of the DMC or equivalent. It ultimately carries the responsibility for deciding whether a trial needs to be modified or stopped on grounds of safety or efficacy.

The TSC will operate in accordance with a trial specific charter. It will meet annually at a minimum but more frequently as requested by the committee, dependent on trial activity or phase.

14.5. Data Monitoring Committee (DMC)

The role of the DMC is to monitor the unblinded trial data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should stop, or aspects of the trial design be amended. This is to safeguard the interest of the participants, investigators and Sponsor. Members of the DMC should be independent of the trial i.e., should not be involved with the trial in any other way or have any competing interest that could impact on the trial.

Reports will be supplied in confidence to an independent DMC, which will be tasked with giving advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet annually at a minimum but more frequently as requested by the committee, dependent on trial activity or phase.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TSC who will convey the findings of the DMC to MHRA, funder, and Sponsor, as applicable.

14.6. Finance

This trial is funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme, award ID: NIHR158535.

14.7. Participant Gratitude and Stipends

Participants will not be paid to participate in the trial.

Parents will be given an (unconditional) £20 voucher with the 2 years of age corrected for prematurity questionnaire, as a token of appreciation for their baby's participation and their time put aside to complete the questionnaire.

15. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 2018, the applicable UK Statutory Instruments, which include the Data Protection Act 2018) and Guidelines for Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations.

The protocol will be submitted to and approved by the REC prior to circulation.

16. Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participants will always be identified using only their unique trial identification number, on the CRF and correspondence between the NCTU and the participating site. Participants will give their explicit consent for the movement of their consent form, giving permission for the Trials Office to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to NCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

NCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those directly involved in the treatment of the participant and organisations for which the participant has given explicit consent for data transfer (e.g. Registries, laboratory staff, competent authority, Sponsor). Representatives of the DEXTA Trial, NCTU and Sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

17. Insurance and Indemnity

The University Hospitals of Derby and Burton NHS Foundation Trust will act as sponsor for the trial. Delegated responsibilities will be assigned to the NHS Trusts taking part, NCTU and SHARP Clinical Services and IPS Pharma. Insurance and indemnity for trial participants and NHS trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96) 48. There are no special compensation arrangements, but trial participants may have recourse to the NHS complaints procedure.

The University of Nottingham has appropriate and typical insurance coverage in place (including, but not limited to Clinical Trials, Professional Indemnity, Employer's Liability and Public Liability policies) in relation to the Institution's Legal Liabilities arising from the University's activities and those of its staff, whilst conducting University business and research activity.

The University Hospitals of Derby and Burton NHS Foundation Trust is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

18. Publication Policy

Results of this trial will be submitted for publication in a high-impact peer-reviewed journal. The manuscript will be prepared by the CI and the members of the TMG, and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the CI or delegate and the NCTU. Manuscripts must be submitted to the CI and the NCTU in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of University Hospitals of Derby and Burton NHS Foundation Trust and funded by the NIHR EME Programme (NIHR158535). This project (NIHR158535) is funded by the [Efficacy and Mechanism Evaluation (EME) Programme], an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care." Further information can be found on our website here, https://www.nihr.ac.uk/about-us/who-we-are/policies-and-guidelines/acknowledging-nihr/programmes.

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Appendix 1

Doses used, treatment duration and reported adverse events for continuous intravenous dexmedetomidine in neonates

Reference	Study design	No. on DexMed	Population	Loading dose (LD) (µg/kg)	Maintenance dose (µg/kg/hr)	Max dose (µg/kg/hr)	Duration of treatment	Adverse events
	PK Studies							
Chrysostomou, 2014	Phase II/III safety, efficacy and PK study	42	28 to 44 wks GA	Dose 1: 0.05 Dose 2: 0.1 Dose 3: 0.2	Dose 1: 0.05 Dose 2: 0.1 Dose 3: 0.2	0.2	6 to 24 hr	No serious AEs No discontinuation
Van Dijkman, 2019	Pilot dose-finding study PK model elaboration	16	Pilot: 34 to 44 wks PMA Validation: 34 to 40 wks PMA	Pilot: no LD Validation: LD (no value)	Pilot: 0.3 Validation: 0.4	0.3 0.4	24 hr	1 case of bradycardia and was resolved when rate was halved
	Randomised controlled trial							
Zedan 2020	Double-blind, randomised controlled trial (DexMed vs Placebo)	20	Mean: 28.05 wks GA (SD: 1.88)	0.1	0.1	0.1	24 hr	No significant difference compared to placebo group regarding adverse effects, including fits, tachycardia, bradycardia, and hypotension
	Observational studies							

O'Mara 2009	Case report	1	24 wks GA DexMed initiation: 9 days PNA	0.5	Range: 0.25 - 0.7	0.7	19 days	No significant adverse effects attributed to DexMed
O'Mara 2012	Retrospective case control study (DexMed vs fentanyl)	24	Mean: 25.5 wks GA (SD: 1.7) DexMed initiation: PNA < 48 hr	Approx. 50% with LD: 0.5	Mean: 0.6 Range: 0.3-1.2	1.2	Mean: 12 days	No bradycardia, no hypotension, no withdrawal syndrome
Estkowski, 2015	Retrospective descriptive study	28	> 37 wks GA	No	Median: 0.4 IQR: 0.26-0.6	1	Median: 38.5 hr IQR: 14.8-69.8 hr Max: 121 hr	2 (7%) bradycardia, 4 (14%) hypotension, DedMed discontinued in 4 (14%) because of cardiovascular AE
Dersch-Mills 2019	Retrospective descriptive study	38	Pre-term (n=17) Median = 30.1 wks GA IQR: 26.1-34 Term (n=21) Median = 38.1 wks GA IQR: 37.5-39.1	No	Preterm Median: 0.5 IQR: 0.3-0.7 Term Median: 0.6 IQR: 0.4-0.7	Not reported >0.7	Preterm Median: 147 hr IQR: 30-482 Term Median 191 hr IQR: 68-326	2/37 (5%) HR < 100 bpm 7/35 (20%) Severe bradycardia (-40 bpm/baseline) 15/36 (42%) hypotension

			DexMed initiation: Pre-term (n=17) Median = 37.9 wks PMA IQR: 31-41.1 Term (n=21) Median = 39 wks PMA IQR: 38.5-40.7 Surgical (79%)					No discontinuation of DexMed 12/27 (44%) had signs of withdrawal
Morton 2021	Quality improvement initiative	173 sedation episodes	Mean: 35.1 wks GA Range: 23-42 DexMed initiation: 34-70.3 wks PMA	No	Median: 0.5 Range: 0.2-0.7	2	Mean: 6.3 days	1 bradycardia 1 treatment interruption due to bradycardia
Tauzin 2022	Retrospective computerized -prescription based study	41	< 45 wks PMA	N=27 (66%) Median: 0.05 IQR: 0.05-0.05	Median: 0.17 IQR: 0.11-0.20	0.28	Median: 6 days IQR: 5-12	Not reported

Dersch-Mills 2022	Retrospective study with matched historical controls	28	Median: 37.3 IQR: 32.7-38.4 <u>DexMed initiation</u> Mean: 38.2 wks PMA SD: 4.5	No	Mean: 0.54 SD: 0.56	0.8	Mean: 343 hr Range: 6–1392 hr	Not reported
Nakauchi 2023	Retrospective before/after study	33	Median: 25 wks GA IQR: 24-26 <u>DexMed initiation:</u> < 24 hr after birth	No	Mean: 0.43	Not reported	Median: 91 hr	No difference in the composite outcome of death between dexmedetomidine and fentanyl
Guillen-Hernandez 2023	Retrospective cohort study	105	<1kg (n=59) Median: 24 wks GA IQR: 24-25 ≥1kg (n=41) Median: 32 wks GA IQR: 29-35 <u>DexMed initiation:</u> <1kg (n=59)	No	Median: 0.4 IQR: 0.3-0.45	<1kg Median: 0.4 IQR: 0.3-0.6 ≥1kg Median: 0.4 IQR: 0.3-0.4	<1kg Median: 9 days IQR: 5-17 ≥1kg Median: 4 days IQR: 3-11	34 (31%) Hypotension 42 (40%) Bradycardia

			Median: 10 days PNA IQR: 2-20 ≥1kg (n=41) Median: 2 days PNA IQR: 0-5					
Irving 2024	Retrospective cohort study with a control group	29	Median: 25.7 wks GA IQR: 25.1–26.7 <u>DexMed initiation:</u> Median: 29.4 wks PMA IQR: 28.3–30.7	0.05	Median: 0.25 IQR: 0.2–0.3	0.4	Median: 6 days IQR: 4.9–8.9	No treatment interruption was observed due to adverse effects
Kayki 2025	Retrospective cohort study	383	Preterm (n=140) Median: 32 wks GA IQR: 28-36 Term (n=243) Median: 38 wks GA IQR: 37-39 <u>DexMed initiation:</u>	No	<u>Initial dose</u> Preterm Mean: 0.32 SD: 0.3 Term Mean: 0.29 SD: 0.2	Preterm Mean: 0.48 SD: 0.59 Term Mean: 0.43 SD: 0.26	Preterm Mean: 6.6 days SD: 7.4 Term Mean: 6.2 days SD: 6.8	4 (3%) bradycardia 4 (3%) hypotension 3 (2%) intervention due to adverse effects No association of max dose with adverse effects (multivariate analysis)

			Preterm (n=140) Median: 14 days PNA IQR: 3-30 Term (n=243) Median: 8 days PNA IQR: 3-15					
Sullivan 2025	Retrospective cohort study	100	Mean: 27.7 wks GA SD: 4 DexMed initiation: Mean: 29.6 wks PMA SD: 3.9	No	Initial dose Median: 0.2 IQR: 0.2-0.3	Median: 0.3 IQR: 0.2-0.4	Analysis at 48 hours	Not reported
Cicalese 2025	Retrospective cohort study Case-matched controls	15	Median: 25.2 wks GA IQR: 24.6, 27.2	No	Initial dose Median: 0.3 IQR: 0.25-0.3	Median: 0.6 IQR: 0.3-1	Median: 30 days IQR: 12.5-54.5	No adverse effects on long-term neurodevelopmental outcomes compared to matched control

Abbreviations: DexMed, Dexmedetomidine; GA, gestational age; IQR, Interquartile range; PMA, postmenstrual age; PNA, postnatal age

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