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SLEEPS: Safety profiLe, Efficacy and Equivalence in Paediatric intensive care Sedation

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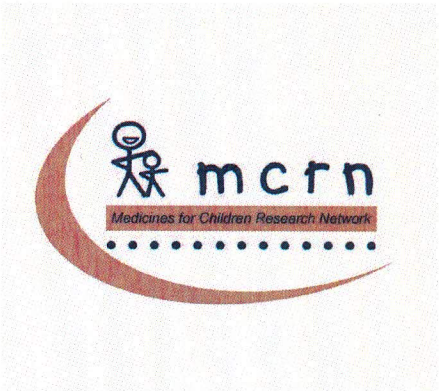
Authorised on behalf of the Sponsor:

Signed: Mary Perkins Date: 18/04/2011

Name MARY PERKINS

Title DEPUTY DIRECTOR of RESEARCH



General Information

This document describes the SLEEPS trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Medicines for Children Research Network Clinical Trials Unit, Liverpool, helpdesk@mcrnctu.org.uk) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the MCRN CTU.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, MCRN CTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

Contact Details: Institutions

Sponsor:	Funder:	Trial Management and Monitoring:
University Hospitals Bristol NHS Foundation Trust, UH Bristol Education Centre, Level 3, Upper Maudlin Street Bristol BS2 8AE. Tel: 0117 342 0233/0266 Fax: 01173420239 E mail: mary.perkins@uhbristol.nhs.uk	NIHR Evaluation Trials and Studies Co-ordinating Centre for Health Technology Assessment, Alpha House, Enterprise Road, University of Southampton Science Park, Southampton. SO16 7NS Tel: 02380 595 586 Fax: 02380 595 639 E mail: hta@hta.ac.uk	Medicines for Children Clinical Trials Unit Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 00 44 (0) 151 282 4528 Fax: 00 44 (0) 151 282 4721 E mail: helpdesk@ mcrnctu.org.uk
Clinical Laboratory (PK/PD):		
Dr Ann Rigby-Jones. N31, ITTC Phase 1 Tamar Science Park 1 Davy Road Derriford Plymouth PL6 8BX Tel: 01752432014 Fax: 01752517984 E mail: ann.rigby-jones @pms.ac.uk		

Details of participating sites can be found in supporting document "Participating Sites"

Contact Details: Individuals

Individuals Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	**Medical Expert who will Evaluate SAE Reports (In absence of CI):**
Dr. Jonathan Sheffield/Mary Perkins/Jake Harley Medical Director/Head of R & D Research and Development University Hospitals Bristol NHS Foundation Trust, UH Bristol Education Centre, Level 3, Upper Maudlin Street Bristol, BS2 8AE Tel: 0117 342 0233/0266 Fax: 01173420239 Email: mary.perkins@uhbristol.nhs.uk	Professor Andrew Wolf Paediatric Intensive Care Unit Bristol Royal Children's Hospital Level 7 Bristol Royal Infirmary Marlborough Street Bristol, BS2 8HQ Tel: 01173428843 Fax: 01173428910 Email: awolfbch@aol.com	Dr Ian Jenkins Paediatric Intensive Care Unit Bristol Royal Children's Hospital Level 7 Bristol Royal Infirmary Marlborough Street Bristol, BS2 8HQ Tel: 01173428843 Fax: 01179268674 Email: ian.jenkins@ubht.swest.nhs.uk OR Dr Margrid Schindler Paediatric Intensive Care Unit Bristol Royal Childrens Hospital Level 7 Bristol Royal Infirmary Marlborough Street, Bristol, BS2 8HQ Tel: 01173428242 Fax: 01179268674 Email : margrid.schindler@UHBristol.nhs.uk
Head of Health Economics:	**Head of Trial Management:**	**Head of Statistics:**
Dr Stavros Petrou Health Economics Research Centre University of Oxford Rosemary Rue Building Old Road Campus Headington Oxford, OX3 7LF Tel: 00 44 (0) 1865 289278 Fax: 00 44 (0) 1865 289701 Email: stavros.petrou@dphpc.ox.ac.uk	Ms Helen Hickey Medicines for Children Clinical Trials Unit Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 00 44 (0) 151 252 5240 Fax: 00 44 (0) 151 282 4721 Email: helpdesk@mcrnctu.org.uk	Dr Carrol Gamble Medicines for Children Clinical Trials Unit Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 00 44 (0) 151 282 4525 Fax: 00 44 (0) 151 282 4721 Email: helpdesk@mcrnctu.org.uk
Health Economist:	**Trial Manager:**	**Statistician:**
Angela Boland Liverpool Reviews and Implementation Group Dept of Pharmacology and Thearpeutics Sherrington Buildings Ashton St Liverpool L69 3GE Tel: 00 44 (0) 151794 5067 Fax: 00 44 (0) 151 794 5585 Email: helpdesk@mcrnctu.org.uk	Ms Catherine Spowart Medicines for Children Clinical Trials Unit Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 00 44 (0) 151 282 *4528* Fax: 00 44 (0) 151 282 4721 Email: helpdesk@mcrnctu.org.uk	Mr Andrew McKay Medicines for Children Clinical Trials Unit Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 00 44 (0) 151 *282 4725* Fax: 00 44 (0) 151 282 4721 Email: helpdesk@mcrnctu.org.uk

Contact Details: Individuals

	Data Manager:	
	Ms Heather Granville Medicines for Children Clinical Trials Unit Institute of Child Health Royal Liverpool Children's Hospital, Alder Hey Liverpool L12 2AP Tel: 00 44 (0) 151 *282 4527* Fax: 00 44 (0) 151 282 4721 Email: helpdesk@mcrnctu.org.uk	

Independent Oversight Committees

Data Monitoring Committee		
Dr Richard Howard Consultant in Paediatric Anaesthesia and Pain Management Department of Anaesthesia GOSH London WC1N 3JH Tel: 02078298865 Fax: 02078298866 Email: r.howard@ich.ucl.ac.uk	Dr Mike Sury Consultant Paediatric Anaesthetist Great Ormond Street Hospital for Children NHS Trust London WC1N 3JH Tel : 0207 829 8865 Fax : 0207 829 8866 Email : SURYM@gosh.nhs.uk	Professor Diana Elbourne Medical Statistics Unit London School of Hygiene and Tropical Medicine Keppel Street London WC1E 7HT Tel: 00 44 (0) 20 7927 2629 Fax: 00 44 (0) 20 7637 2853 Email: Diana.Elbourne@lshtm.ac.uk

Independent Members of the Trial Steering Committee*		
Professor Adam Finn Institute of Child Life & Health UBHT Education Centre Upper Maudlin Street Bristol BS2 8AE Tel: (0117) 342 0168 Fax: (0117) 342 0178 Email: adam.finn@bristol.ac.uk	Dr Kerry Hood, Director/Statistician South East Wales Trials Unit Centre for Health Sciences Research Cardiff University Nenadd Meirionydd Heath Park Cardiff CF14 4YS Tel: 029 2068 7163 Fax: 029 2074 3833 Email: hoodk1@cf.ac.uk	Dr John Henderson ALSPAC, University of Bristol Oakfield House Oakfield Grove Clifton Bristol BS8 2BN Tel: 0117 331 0071 Fax: 0117 331 0080 Email: 'a.j.henderson@bristol.ac.uk'

* Non-independent members listed in section 16

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Glossary

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
ECMO	Extracorporeal membrane oxygenation
GP	General Practitioner
IB	Investigator's Brochure
IDSMC	Independent Data and Safety and Monitoring Committee
ICU	Intensive Care Unit
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
IV	Intravenous
Kg	Kilograms
LREC	Local Research Ethics Committee
Mcg	Micrograms
MCRN CTU	Medicines for Children Clinical Trials Unit
Mg	Milligram
Ml	Millilitre
MREC	Multi-centre Research Ethics Committee
PD	Pharmacodynamic
PI	Principal Investigator
PICU	Paediatric Intensive Care Unit
PK	Pharmacokinetic
R&D	Research & Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
VMA	Urinary Vanillylmandelic acid

1 PROTOCOL SUMMARY

Title: Prospective multi-centre randomised, double-blind, equivalence study comparing clonidine and midazolam as intravenous sedative agents in critically ill children

Phase: III

Population: Children will be recruited from paediatric intensive care units across the United Kingdom. Eligible children will be aged 30 days to 15 years inclusive admitted to PICU and likely to require intubation and ventilation for more than 12 hours, 50kg or less in weight and adequately sedated. Patients will be excluded from study if they have had cardiac surgery without chest closure, suffer from status epilepticus or active fitting, require haemodialysis, haemofiltration or ECMO treatment, have severe neuromuscular problems/impairment, currently require beta blocker therapy or are being chronically treated for raised blood pressure. Additionally, patients with a known allergy to the trial therapies, receiving continuous or intermittent muscle relaxants, patients who are pregnant or suffering from acute traumatic brain injury will be excluded.

Number of Sites: This trial will be conducted in 10 of the centres listed in the supporting document "Participating Sites"

Study Duration: Recruitment will take place within 120 hours of arrival in PICU/ICU. Patients will receive their allocated therapy for a maximum of 7 days. Those requiring continued sedation will then transfer to an alternative therapy, as per individual unit policy, in accordance with established clinical practice of "drug cycling". All patients will be followed up from randomisation until hospital discharge.

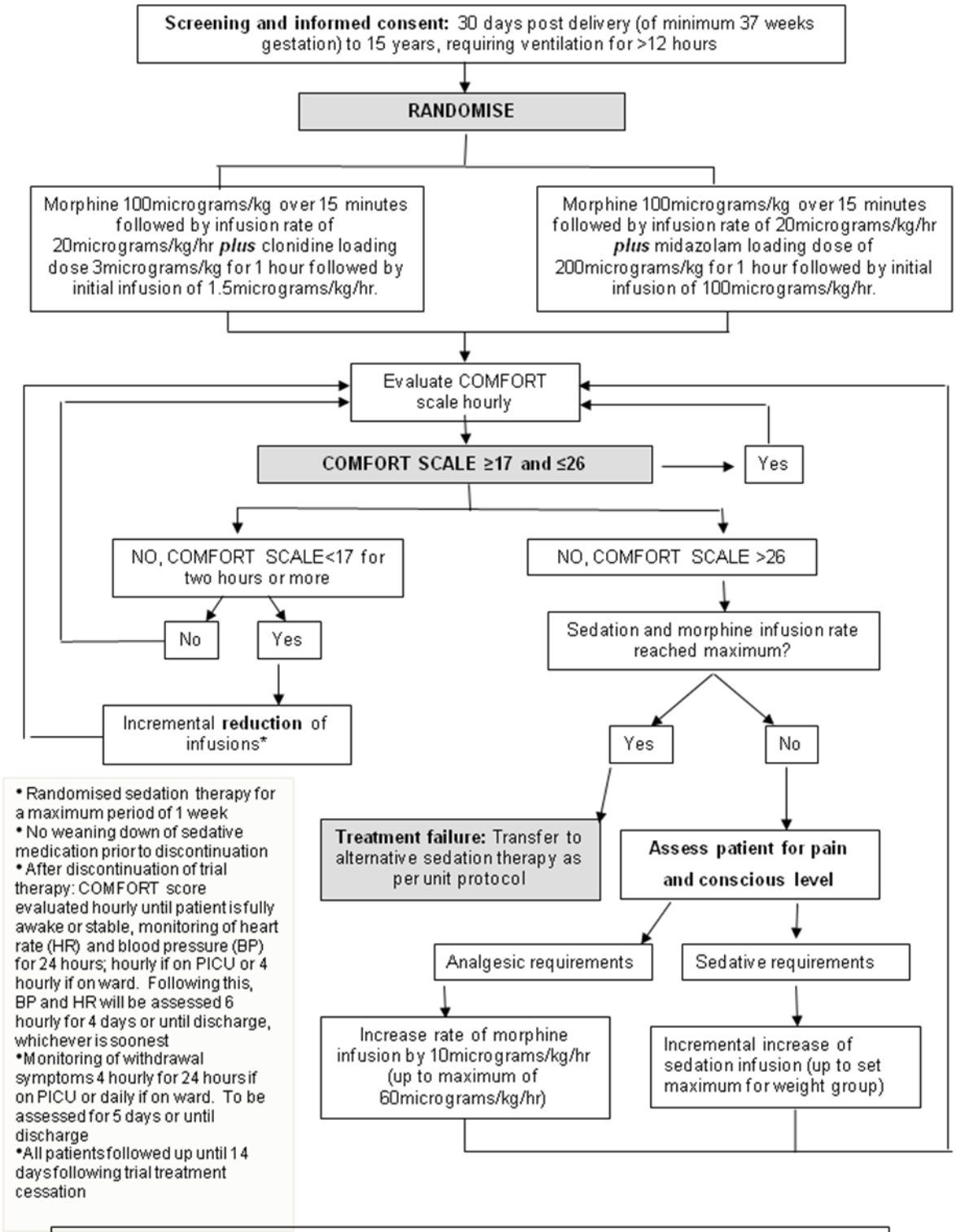
Description of Intervention: A loading dose of clonidine 3 micrograms/kg or midazolam 200 micrograms/kg will be given over the first hour of treatment, prepared using the next appropriate pre-randomised, sequentially numbered, blinded treatment pack containing blinded ampoules of either midazolam or clonidine. Concentrations in the allocated treatment packs will allow administration of either clonidine or midazolam at comparable rates for each weight range (maintaining blinding), and provide the range of doses chosen (0-3 micrograms/kg/hr clonidine or 0-200 micrograms/kg/hr midazolam). Both treatment groups will also receive Morphine 100 micrograms/kg over 15 minutes at the outset of the study, followed by an infusion with morphine, commencing at 20 micrograms/kg/hr. After the one hour loading period the clonidine and midazolam infusions will continue at maintenance doses (1.5 micrograms/kg/hr clonidine or 100micrograms/kg/hr midazolam). Subsequent delivery of the clonidine or midazolam will be adjusted according to behavioural assessment. There is provision for increasing the morphine dose to a maximum of 60micrograms/kg/hr if necessary.

Primary Objective: To determine whether intravenous clonidine can provide equivalent control of sedation in the critically ill child when compared to intravenous midazolam

Secondary Objectives: (1) To determine whether clonidine reduces side-effects and improves clinical outcomes due to its effects on reduction of sympathetic outflow, improved organ perfusion and protection in ischaemic reperfusion injury;

(2) To provide a detailed description of pharmacokinetic variables for clonidine and midazolam and their relationship with pharmacodynamic effects in critically ill children.

Protocol Summary - continued



*If a COMFORT score <17 is recorded for two consecutive hours then reduce morphine or trial sedation as clinically indicated incrementally down to 20micrograms/kg/hr of morphine and to the minimum trial infusion rate for the weight group. If minimum trial infusion rate is administered and the morphine infusion rate is 20micrograms/kg/hr and the child still has a COMFORT score below 17, then if there are no analgesic requirements, the morphine can be further decreased by an increment to10micrograms/kg/hr. If the COMFORT score is still below 17, the morphine can be stopped (providing there are no analgesic requirements. If the COMFORT score is still below 17, the trial sedation can be temporarily stopped until the COMFORT score rises to 17 or more.

2 BACKGROUND INFORMATION

2.1 Introduction

Approximately 2% of all children admitted to hospital require paediatric intensive care unit (PICU)[1]. Most of these critically ill children will require potent analgesic and sedative drugs to facilitate artificial ventilation, alleviate pain and prevent discomfort from procedures such as cannula placement, physiotherapy and endotracheal suctioning. Sedation is needed to prevent distress from the presence of unfamiliar personnel and from the high level of background noise, which can disturb natural sleeping patterns[2]. In the critically ill child, sedative and analgesic drugs are usually given during the acute phase of the illness by intravenous infusions on a standardised dose per weight basis, which are then adjusted according to observation of physiological and behavioural criteria.

Undersedation and oversedation are both harmful. Inadequate sedation is unacceptable in a vulnerable child that may be unable to move or communicate its distress due to use of muscle relaxants, while the unparalysed child may "fight" the ventilator leading to ineffective ventilation, accidental extubation or the loss of invasive access or monitors. In intensive care, agitation and inadequate sedation has been correlated with adverse short term and longer term outcome[3]. In contrast, oversedation delays recovery, promotes tolerance to the drugs and leads to distressing symptoms on withdrawal of the drugs (agitation, seizures, hallucinations, psychosis, fever and tachycardia)[4].

Benzodiazepines

Midazolam has been the most popular sedative used in critically ill children in the UK. It is usually given in combination with an opioid by intravenous infusion at doses between 50-300micrograms/kg/hr[10]. Alternative agents to midazolam include diazepam, clonidine, chloral hydrate and promethazine. The limited data on midazolam suggest a high incidence of side effects: in two studies designed to observe adverse reactions to sedative agents[11,12] the reported incidence was as high as 35% for midazolam, and this was related to duration of the infusion and cumulative dose. The duration of abnormal behaviour after drug withdrawal was as long as 1 week. Limiting the benzodiazepine dose may delay the onset of tolerance, but is often unobtainable because of the need to maintain adequate sedation. Furthermore in a more recent study on neonatal sedation and neurological outcome the use of midazolam appeared to have an adverse effect on outcome compared to morphine or placebo[13]. This has led to a significant reduction of midazolam use in the neonatal intensive care. The intrinsic effects of midazolam and morphine on outcome have never been compared to other regimens.

Clonidine

Clonidine is a lipid soluble, partial alpha-2 agonist with antihypertensive, analgesic and sedative effects. Its primary antihypertensive action is attributed to its central alpha-2 effect on the sympathetic outflow resulting in reduced heart rate, vasodilation and lowered blood pressure[12]. More recently it has gained recognition for its sedative and analgesic properties. The mechanism for the sedative and analgesic actions actions is not clear but is thought to be a combination of central effects that modulate descending inhibitory nociceptive mechanisms and spinal analgesia acting on the dorsal horn of the spinal cord[13]. Elimination is through both hepatic metabolism to inactive metabolites and direct renal excretion[14].

Caudal epidural and spinal clonidine has been evaluated in paediatric anaesthesia. It has been shown to augment pain relief and increase the duration of postoperative analgesia with minimal side effects[17-19] and is now used routinely in paediatric practice. Given as an oral premedicant, clonidine has similar anxiolytic and sedative properties to preoperative benzodiazepines[20] but in addition it can attenuate haemodynamic responses to nociception

and provide postoperative analgesia. These effects on central sympathetic outflow and centrally based analgesia mechanisms reduces intraoperative anaesthetic requirements and metabolic responses to surgery [21]. In anaesthesia of the critically ill neonatal cardiac patient this has shown to have improved outcome in terms of survival[22].

In the last 5 years, following experience with clonidine in paediatric anaesthesia and its use in adults withdrawing from alcohol and opioids it has become increasingly used for sedation and analgesia in the critically ill child in PICU[23]. However, despite its widespread use there are few data on effectiveness, dose requirement and safety. A limited dose finding study in PICU has demonstrated that it can provide dose dependant sedation in place of morphine using an intravenous infusion rate of 1-2 micrograms/kg/h without haemodynamic compromise in terms of heart rate blood pressure or cardiac output [24]. A small prospective study of critically ill children demonstrated that concomitant administration of oral clonidine significantly reduces morphine and lorazepam requirements without additional side effects [25].

Possible beneficial effects
The reduction of sympathetic outflow associated with clonidine may have specific benefits to critically ill children in PICU. Studies in animals suggest that alpha-2 agonists can improve neurological outcome associated with ischaemic cerebral injury[26-30]. These beneficial effects are alpha-2 specific and reversed with selective alpha-2 antagonists[28]. The protective mechanism of action is unclear but may be due to suppression of extracellular glutamate and aspartate release during energy failure[31]. Recent data has also demonstrated that pre-conditioning before the insult can both reduce infarct size and improve neurological outcome after insult [30].

Trauma surgery and critical illness are associated with a variety of neuro-humoral responses (the stress response), which can result in organ dysfunction[32]. More specifically, renal function deteriorates after both adult and paediatric cardiac surgery, and this effect is due in part to the increase in sympathetic outflow and the rise in circulating vasoconstrictors such as noradrenaline, vasopressin and angiotensin[33,34]. Clonidine has been demonstrated to suppress these responses and prevent the associated decline in renal function after adult cardiac surgery [35]. In addition, clonidine has independent local effects on tubular function which promote both diuresis and natriuresis[36]. In terms of cardiovascular responses, reduction in stress responses by alpha-2 agonists have been shown to reduce perioperative myocardial ischaemia in adults undergoing both cardiac and non-cardiac surgery[37].

Toxicity
Clonidine can cause significant side-effects after accidental overdose in children: pallor, bradycardia, hypotension, miosis, unconsciousness, hypotonia and hypothermia[38,39]. In adults the peripheral alpha-1 effects can cause hypertension and vasoconstriction in overdose, but this appears to be far less common in children. Importantly, in terms of safety, even gross overdose does not appear to be lethal. The only deaths in the literature have been associated with multiple drug ingestion and were not thought to be related to clonidine[40]. The highest overdose reported was a 1000 fold overdose in a 5 year old child who was given 50 mg of clonidine and discharged uneventfully after 42 hours[41].

2.2 Rationale

Although, there are few data on the use of clonidine in paediatric intensive care, this drug has been adopted widely in PICU as a mainstream sedative agent and as a treatment for drug withdrawal in children after prolonged exposure to sedatives[23]. Clonidine has specific attributes that make it potentially a better choice than midazolam as an adjunct to morphine:

co-analgesia through a different mechanism than opioids, reduction in sympathetic tone, improved cardiac and renal function, protection from ischaemic/reperfusion injury and reduced tolerance/withdrawal. The combination of morphine and clonidine seems to be a rational alternative to the current use of morphine and midazolam. Given these theoretical advantages and limited clinical information on the use of alpha-2 agonists for sedation in PICU, there is a need to evaluate this drug objectively and to determine if it has outcome benefits compared to the routine use of midazolam.

It could be argued that a limited pilot study might be more appropriate to determine safety and efficacy before engaging in a larger study. However we believe that a full study at the outset is justified. A previous pilot data set defined dose effectiveness of intravenous clonidine which allows assumptions of dose equivalence of midazolam with clonidine[24]. For clonidine, an ED 95% for the COMFORT score in the effective range was provided by an infusion rate of 2micrograms/kg/hr. This compares to an effective range of 50-200micrograms/kg/hr for midazolam[11,12] with an ED95% of 150micrograms/kg/hr. Moreover, clonidine is being used widely in paediatric intensive care but without any benchmark data. There is an urgent need to define safety and efficacy in a larger group of patients and in a more rigorous fashion than the previous pilot studies. A definitive study needs the resources of several centres to achieve this, and given the difficulties in obtaining adequate patient numbers we believe that a fully monitored study at the outset is the appropriate ethical approach to achieve firm conclusions rapidly and avoid the dangers described above of adopting new drugs in the critically ill without appropriate evaluation.

Quite apart from the issue of quality of sedation, and potential cost savings by avoiding complications associated with sedation and analgesia in PICU, the use of IV clonidine provides modest cost savings over IV midazolam. The cost of midazolam at 150micrograms/kg/hr is currently £1-60p per day for the drug compared to 90p per day for 2micrograms/kg/hr of clonidine[42].

2.3 Objectives

Primary Objective

To determine whether intravenous clonidine can provide equivalent control of sedation in the critically ill child when compared to intravenous midazolam

Secondary Objective:

To determine whether clonidine reduces side-effects and improves clinical outcomes due to its effects on reduction of sympathetic outflow, improved organ perfusion and protection in ischaemic reperfusion injury.

2.4 Potential Risks and Benefits

Both midazolam and clonidine are regularly used as intravenous sedative agents in the paediatric intensive care environment, administered as part of standard care, to critically ill children requiring sedation, and therefore patients are not exposed to any increased risk as a result of this research. The known potential risks of these drugs will be fully explained and verbal information will be reinforced with the provision of a written leaflet, approved by the appropriate ethical committee. Due to the necessity of providing a blinded format for the trial design, the treatments are being manufactured at concentrations that will employ identical volumes of sedative per infusion for both treatment arms. In order to facilitate equivalent volumes of the two sedatives, it has been necessary to create a formulation of midazolam that is not available commercially. Clonidine remains in the concentration that is commercially available but is manufactured for the trial and packaged in containers specifically for the trial in order that trial blinding can be effective. The manufacture of the

trial treatments is being carried out by SCM Pharma, 6 Regent Drive, Low Prudhoe Industrial Estate, Northumberland NE42 6PX. The blinded 5ml ampoules will contain either 150 mcg/ml of clonidine or 10mg/ml of midazolam. These ampoule concentrations have been chosen so that the drug infusions made up from the ampoules will deliver clinically relevant doses of the drugs to that used in everyday clinical practice for control of sedation in paediatric intensive care. The doses delivered according to the protocol from the ampoules (either clonidine or midazolam) have been chosen to provide equivalent sedation based on the known literature on use of these drugs in intensive care:

Clonidine will be infused according to the protocol at doses ranging from 0.75-3mcg/kg/hr (see section 7.4.1). This intravenous dose range is based on studies that have evaluated sedation quality and cardiovascular effects in PICU. The available data indicates in this dose range adequate sedation is likely to be obtained without significant side effects (23,24,25)

Midazolam will be infused according to the protocol at doses ranging from 50-200mcg/kg/hr (see section 7.4.2). This intravenous dose range is based on studies that have evaluated sedation quality and side effects in PICU. The available data indicates that in this dose range adequate sedation is likely to be obtained without significant side effects (11,12,23)

2.5 Potential Risks of Clonidine

2.5.1 – Side effects described by summary of product characteristics

In adults, side effects reported in the summary of product characteristics (SmPC) provided by the sole commercial manufacturer (Bohringer) include:

General: A variety of symptoms such as sedation, dry mouth and with withdrawal, agitation, constipation, nausea and vomiting, headache, malaise, impotence, decreased libido, gynaecomastia and paraesthesia of the extremities have been reported. Pain in the parotid gland, drying out of the nasal mucosa and reduced lachrymal flow (caution: contact lens wearers) as well as skin reactions with symptoms such as rash, urticaria, pruritus and alopecia have also been observed.

Cardiovascular
Side effects reported include fluid retention, orthostatic hypotension and associated dizziness, Raynaud's phenomenon, peripheral vasoconstriction and ECG abnormalities. In very rare cases clonidine may cause or potentiate bradyarrhythmic conditions such as sinus bradycardia or AV-block.

Nervous System Sleep disturbances, nightmares, depression, perceptual disorders, hallucinations, confusion and disturbances of accommodation may occur.

Gastrointestinal and Hepatic System Abnormal liver function tests have been reported occasionally and two cases of hepatitis have been reported. Rarely, pseudo-obstruction of the large bowel has been observed.

Metabolic Acute administration of clonidine hydrochloride in animals or in man have been reported to occasionally induce a transient elevation of blood sugar. This is believed to be due to the initial pharmacological effect of alpha-adrenergic stimulation. Investigators agree that this has no clinical significance. The inclusion of diabetic patients in many clonidine

hydrochloride investigations has confirmed its suitability as an antihypertensive agent for such patients.

Overdose
In overdose, manifestations of intoxication are due to a generalised sympathetic depression and include pupillary constriction, lethargy, bradycardia, hypotension, hypothermia, coma and apnoea. Paradoxical hypertension caused by stimulation of peripheral alpha$_1$-receptors may occur. In most cases, general supportive measures will be sufficient to treat an overdose. Severe bradycardia may be treated with adrenaline or other chromotropic drugs.

2.5.2 Side Effects and Expectedness with Clonidine in PICU

Despite this drug being used widely in PICU and general paediatrics in the last few years, there are few reports of major side effects or major adverse events. Side effects appear to be more common and marked in adults than in children. Much of the data on side effects in children are derived from reports of overdose after accidental ingestion. Side effects reported after accidental overdose of clonidine in children include pallor, bradycardia, hypotension, miosis, unconsciousness, hypotonia and hypothermia and reduced ventilatory drive/ apnoea [38,39]. An overdose of 1000 fold in a 5 year old child has previously been published and has shown the drug to be very safe as the child was discharged uneventfully after 42 hours[41]. A recent drug error soon to be published resulted in 100 times dosage being given caudally in three patients sequentially without incident (personal communication editor Pediatric Anesthesia : in Press).

The following side effects are mentioned with regards to their relevance to the study:

Bradycardia and hypotension: In the trial, bradycardia and hypotension may occur with higher doses of the infusion rate but they appear to be much less common than the events reported in adults. While the effect is likely to be dose dependant there is considerable individual variability in response.

Cardiac dysrythmias: While this is a known side effect it would not be expected to occur commonly if at all during the trial. Cardiac dysrythmias such as AV conduction block would be regarded as an expected serious adverse reaction and would be reported as such.

Rebound hypertension: After longer term use of clonidine (days and weeks) rebound hypertension has been described in adults. There is anecdotal evidence that it may occur in children, but no published data to date. The trial design of SLEEPS, which has a maximum duration of trial treatment of 7 days, should identify any incidence of this event within a controlled environment if it should occur.

Pseudo-obstruction of the large bowel: Pseudo-obstruction of the large bowel (listed in the SmPC) has not been reported in children and would not be expected.

Hypertension and hypotension: Acute hypertension due to the early peripheral alpha -1-agonist effect that preceeds the central alpha -2-effect has been described occasionally in adults with rapid intravenous injection of the drug. This phenomena on initiation of drug treatment with intravenous clonidine has not been seen in clinical practice in PICU. The loading dose of clonidine for the SLEEPS study is 3mcg/kg given over one hour and is not expected to produce either hypertension or hypotension.

All other observed side effects not identified in 2.51 and 2.5.2 with use in PICU will be reported as unexpected.

2.6 Potential risks of Midazolam

2.6.1 Side effects described by the summary of product characteristics

The following adverse reactions of midazolam have been reported in the SmPC by Roche Products LTD UK (the major medical manufacturer of this drug) as rare complications associated with intravenous midazolam injection in adults and children:

Immune System Disorders: Generalised hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), anaphylactic shock.

Psychiatric Disorders: Confusional state, euphoric mood, hallucinations.

Paradoxical reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, hostility, rage reaction, aggressiveness, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

Dependence: Use of midazolam - even in therapeutic doses - may lead to the development of physical dependence. After prolonged i.v. administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions.

Nervous System Disorders: Prolonged sedation, decreased alertness, somnolence, headache, dizziness, ataxia, postoperative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported. Convulsions have been reported in premature infants and neonates.

Cardiac Disorders: Severe cardiorespiratory adverse events have occurred. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered.

Respiratory Disorders*:* Severe cardiorespiratory adverse events including respiratory depression, apnoea, respiratory arrest, dyspnoea, laryngospasm have been reported. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered. Hiccup.

Gastrointestinal System Disorders: Nausea, vomiting, constipation, dry mouth.

Skin and Appendages Disorders: Skin rash urticaria, pruritus.

General and Application Site Disorders: Fatigue, erythema and pain on injection site, thrombophlebitis, thrombosis.

Overdose: This seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnoea, hypotension, cardiorespiratory depression and in rare cases to coma. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory

disease. If overdose were to occur, then the patient's vital signs should be monitored and if required, general supportive measures should be implemented. A specific antagonist that acts as an antidote (Flumazanil) is available but is rarely used in overdose. Patients should be monitored closely if flumazanil is administered and should be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepresaants).

2.6.2 Side Effects and Expectedness with Midazolam in PICU

Although the above side effects have been reported with midazolam in the wider practice and administration with this drug, it is a drug that has been used for more than 15 years in sedation of the critically ill child. When used as a sedative drug in PICU, the following side effects are common and will be explained with regards to relevance to the study:

Hypotension and bradycardia: Hypotension and bradycaria are both expected side effects that can occur particularly on first exposure or with larger loading doses. This effect is dose dependant but has considerable individual variability. In usual practice and with doses proposed in the SLEEPS study it is unlikely to be sufficient to require medical intervention. Data on this will be captured as part of the study.

Reduced ventilatory drive: This can occur during midazolam administration, particularly on loading. Children entered into the study will already be mechanically ventilated and any reduction in ventilatory drive either during loading or the subsequent infusion will be identified. This is an expected side effect although it is considered that inhibition of ventilatory drive may occur, the effect will be small and unlikely to require intervention. If intervention is required then this should be reported as an adverse event.

Withdrawal phenomena: On cessation of the drug withdrawal phenomena including agitation, hypertension, abnormal behaviour and tremors are relatively common and has been reported in as much as 30% of patients in one study (12), therefore would be classified as expected side effects. All withdrawal symptoms will be recorded for 5 days following treatment cessation on a withdrawal symptoms chart and also on the adverse event page of the Case Report Form (CRF).

Tolerance: The drug becomes less effective with time (tolerance) and can produce severe withdrawal effects particularly associated with total amount of the drug given (both higher doses and longer duration of exposure) (23).

The above side effects mentioned in relation to PICU use are expected but with the exception of withdrawal phenomena are mild and would require little or no intervention. Withdrawal phenomena are common, idiosyncratic and can on rare occasions be quite severe requiring medical interventions. If an intervention is required to treat a withdrawal symptom this will be recorded on the withdrawal symptoms chart.

The other side effects documented in the SmPC are rare and unpredictable therefore would not be expected in PICU use although if any of these were to occur they should still be reported as an adverse event

2.6.3 Reporting requirements

Any untoward and unintended response that occurs in a participant in the trial that is suspected to be related to any dose administered of either Midazolam or Clonidine will be considered to be a suspected adverse reaction and must be reported.
All adverse reactions suspected to be related to either of the trial treatments should be reported on the Adverse Reaction Case Report Form, however for ease of completion a list of known adverse reactions will be provided on this CRF; the list will comprise of the following:

- Hypotension that requires intervention
- Bradycardia that requires intervention
- Hypertension following cessation of trial treatment

Non-serious adverse events that are considered by the local investigator or local research nurse to be unrelated to trial medication do not need to be reported.

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that fulfil the criteria of a serious event (see section 10.1) must be reported using the Serious Adverse Event CRF, regardless of whether they are suspected to be related to the administration of Midazolam or Clonidine.

Signs and symptoms will be graded and reported as; mild symptoms (score 1); moderate symptoms (score 2) and severe symptoms (score 3). Seriousness and causality will also be assessed by the reporting researcher (see section 10).

All Adverse Reactions, Serious Adverse Events, Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions will be recorded from randomisation until 14 days following cessation of trial treatment. Please see section 10 for further details of reporting procedures and requirements.

2.7 Known Potential Benefits

Both midazolam and clonidine are currently used in routine practice for sedation in PICU. The potential benefits of this trial is in terms of side-effects over conventional practice for critically ill children, defining dosing regimens based on drug action and pharmacokinetics and enabling an evidence based decision to be made when selecting an appropriate sedative agent to be administered in this vulnerable population.

2.7.1 Clonidine

Clonidine was initially introduced in PICU as a drug to ameliorate the effects of opioid withdrawal based on adult experience with opioid abuse. It subsequently became clear that the drug was effective in providing dose dependant sedation with few major side-effects. Reviews, case reports and small scale studies have suggested that using the drug as a sedative in PICU is not associated with the major problems of tolerance and withdrawal side –effects, although no large objective study has yet been done. It has been shown to have benefits on cardiovascular regulation and outcome through reduction of sympathetic tone. Renal function after surgery is also improved by the use of alpha-2-agonists and animal studies have shown the drug to provide some protection against hypoxic reperfusion injury.

2.7.2 Midazolam

Midazolam has been used for longer and therefore there are more data on dose requirements, risks and benefits. Midazolam is beneficial to the critically ill child by providing sedation. However, the development of tolerance and withdrawal effects as detailed above means that an effective alternative therapy is desired.

3 SELECTION OF CENTRES/CLINICIANS

3.1 Centre/Clinician Inclusion Criteria

a. Regional paediatric intensive care unit
b. Able to recruit a minimum of 84 patients in 2 years
c. Local Principal Investigator who acknowledges and agrees to conform to the administrative and ethical requirements and responsibilities, in compliance with Good Clinical Practice and regulatory requirements
    - ensuring that sufficient time, staff and adequate facilities are available for the trial, including local training on COMFORT score, with in house validation of a team of nurses who can oversee data acquisition
    - provide information to all supporting staff members involved with the trial or with other elements of the patient's management
d. Local pharmacy department with capability to provide trial supplies as per protocol, including appropriate facilities for storage and distribution
e. Positive Site Specific Assessment by LREC or by local Research and Development Department
f. Local Research and Development approval
g. Receipt of evidence of completion of (d) & (e) by MCRN CTU
h. Completion and return of 'Signature and Delegation Log' to MCRN CTU

3.2 Centre/Clinician Exclusion Criteria

a. Unable to fulfil inclusion criteria

4 TRIAL DESIGN

4.1 Primary Endpoint

1. The primary endpoint is adequate sedation defined as at least 80% of total time spent sedated within a COMFORT score range of 17 to 26.

4.2 Secondary Endpoint(s)

During study treatment phase

1. Percentage of time spent adequately sedated
2. Time to reach the maximum permitted dose of sedation
3. Time to reach the maximum permitted dose of morphine
4. Profile in rise of daily cumulative sedative infusion
5. Profile in rise of daily cumulative morphine infusion
6. Maximum permitted dose of sedative reached
7. Maximum permitted dose of morphine reached
8. Fall in blood pressure judged by clinician to require intervention
9. Increased inotropic support required in 1st 12 hours after randomisation
10. Supplementary analgesia required during sedation
11. Daily urine output
12. Treatment failure defined as inadequate sedation after one hour of maximum doses of sedative and morphine infusions (determined by a COMFORT score above 26) or treatment failure defined as three *'events' where rescue medication(s) are needed to re-establish sedation or pain control occuring within any one 12 hour period during trial treatment
13. Blood biochemistry and urinalysis
14. Urinary concentration of gamma glutamyl transpeptidase (Bristol only)
15. Urinary concentration of alkaline phosphatase (Bristol only)

* An 'event' is described as a point when control of sedation is deemed to be acutely lost requiring immediate intervention. The intervention can involve more than one drug given over a short period of time to establish rapid control (within approximately a 30 minute window to allow safe titration if necessary).

Following study treatment phase

16. Time from stopping all sedation to being fully awake (determined by a sustained** score of 4 on the alertness category of the COMFORT score)
17. Rebound hypertension
18. Signs of withdrawal measured using a 11 point assessment for abnormal behaviour (to be recorded until 5 days following trial treatment cessation or until discharge, whichever is soonest)
19. Withdrawal symptoms requiring clinical intervention (to be recorded until 5 days following trial treatment cessation or until discharge, whichever is soonest)

** Sustained for 2 hours or more.

Throughout the duration of study

20. Adverse events (to be recorded until 14 days post trial treatment cessation)

Health Economics

21. Cost per additional case of adequate sedation.

5 STUDY POPULATION

5.1 Inclusion Criteria

a. Children aged 30 days (37 weeks gestation or greater) to 15 years inclusive. Children born before 37 weeks gestation are eligible if they are a minimum of 30 days post delivery and their corrected gestation is 37 weeks or more.
b. Admitted to PICU, ventilated and likely to require ventilation for more than 12 hours.
c. Recruitment within 120 hours of arrival in PICU/ICU.
d. Child is 50kg or less in weight
e. Able to perform a COMFORT score on the child
f. Adequately sedated: COMFORT score within the range of ≥17 and ≤ 26
g. Fully informed written proxy consent

5.2 Exclusion Criteria

a. Those patients with open chests following cardiac surgery
b. Those patients chronically treated for raised blood pressure
c. Current treatment with beta blockers (if patients have not received beta blockers for 24 hours prior to entry into the trial then they are eligible to participate)
d. Acute traumatic brain injury
e. Status epilepticus or active fitting (2 or more seizures regularly on a daily basis)
f. Those patients requiring haemodialysis or haemofiltration
g. Those patients requiring ECMO treatment
h. Those patients with severe neuromuscular problems/impairment that you cannot perform a COMFORT score on
i. Known allergy to either of the trial medications (clonidine, midazolam or morphine)
j. Current treatment with continuous or intermittent muscle relaxants.
k. Those patients known to be pregnant
l. Currently participating in a conflicting clinical study or participation in a clinical study involving a medicinal product in the last month
m. Previously participated in SLEEPS trial.

N.B. the use of midazolam or clonidine to establish sedation does not preclude entry into the trial.

5.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient (or parent/legal representative) should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the participant's condition becomes stable.
Follow-up of these patients will be continued through the trial Research Nurses and the lead investigator at each Centre.

5.3.1 Patient Transfers

It is not likely that patients will require transfer to another centre whilst receiving trial therapy. In the unlikely event that a patient would be transferred to another centre during follow-up, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient to enable collection of data relating to heart rate, blood pressure and incidence of suspected Adverse Reactions, or Serious Adverse Events at the very least, or, if this is not possible, for date of hospital

discharge to be collected via their GP. A copy of the CRFs should be provided to the new site if transferred to another participating centre. The patient (or parent/legal representative) will have to sign a new consent form at the new site, and until this occurs the patient remains the responsibility of the original centre. The CTU should be notified in writing of all patient transfers.

If a patient is transferred to another centre (i.e. to a District General Hospital) during follow up then the research nurse will make a daily phonecall to the ward. The research nurse will ask for details of heart rate, blood pressure and withdrawal symptoms for the 5 days following cessation of treatment or until discharge, whichever is soonest.

5.3.2 Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:

a. Parent/ legal representative (or, where applicable, the patient) withdraws consent.
b. Unacceptable toxicity.
c. Intercurrent illness preventing further treatment.
d. Treatment failure as defined in Section 7.
e. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion, including:
    - Need to commence ECMO, haemodialysis or haemofiltration
f. Extubation (or trial of extubation)
g. A requirement for treatment with a beta blocker
h. A requirement for continuous infusion of muscle relaxants

If sedation is stopped before 1 week due to recovery, then the trial medicines should be stopped abruptly and any withdrawal or analgesia issues treated as they emerge. If a parent/ legal representative (or, where applicable, the patient) wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 5.3.3).

Once trial treatment has been discontinued for any reason it cannot be recommenced. Following withdrawal from trial treatment patients will be treated according to local practice and follow-up data collection should proceed as per the trial protocol.

5.3.3 Withdrawal from Trial Completely

Patients are free to withdraw consent at any time without providing a reason. Patients who wish to withdraw consent for the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses. The patient will not contribute further data to the study and the MCRN CTU should be informed in writing by the responsible physician and an End of Study CRF should be completed. Data up to the time of withdrawal will be included in the analyses unless the patient explicitly states that this is not their wish.

6 ENROLMENT AND RANDOMISATION

6.1 Enrolment

Screening will be performed of a patient's possible eligibility for the study and must be documented on the "Screening log". If a patient is assessed to be eligible for the study, the parent or legally acceptable representative of the patient will be issued with the patient information and consent forms (See Table 5. Schedule of Study Procedures).
In each of the participating PICUs, patients will be reviewed by the consultant staff or designated research nurse each morning to identify potential research cases fulfilling eligibility criteria (fully listed in Section 5).

There are some patients who will be scheduled for surgery who would be expected to be eligible for the trial following surgery. When these patients are identified, the parent or legally acceptable representative of the child can be approached prior to surgery and can be given a Patient Information Sheet so that they can consider participation in the trial. If the patient is still found to be eligible upon arrival in PICU then the parents will be approached for consent.

If a patient is identified as being eligible for the trial prior to or during transfer to PICU then the study can be mentioned to the parent or legally acceptable representative prior to or during transfer and they can be given a summary information sheet. The parents would be reapproached when the child is on PICU and they would be given the full patient information sheet on PICU.

To be eligible for the study the child must meet the inclusion and exclusion criteria (See section 5.1 and 5.2). Once a child has been assessed as meeting all the entry criteria and consent has been obtained from the parent or legally acceptable representative the baseline assessments will be carried out.

6.2 Baseline Assessments

1. Medical history (including reason for admission to PICU) will be recorded
2. Current and previous sedation therapy and analgesic therapy will be recorded, (including dose and date/time commenced).
3. A COMFORT score will be recorded
4. Blood pressure and heart rate
5. Baseline bloods (Sodium, potassium, chloride, urea, creatinine, bilirubin, ALT/AST, Alkaline phosphatase).
6. PELOD score (measure of severity of illness calculated using routine PICU measurements)

The randomisation process will occur once:
1. Eligibility criteria has been fulfilled
2. Fully informed written proxy consent

The baseline assessment section of the randomisation CRF can be completed retrospectively

6.3 Randomisation Process (T0)

1. Completion of Randomisation CRF and trial prescription

2. Allocation of pre-randomised pack (next in appropriate sequence); to be randomised and treatment commenced within 24 hours of consent being taken.
3. Submission of Randomisation CRF and allocation notification to MCRN CTU within 7 days of randomisation
4. Forward copy of consent/assent forms to MCRN CTU within 7 days of randomisation

7 TRIAL TREATMENT/S

7.1 Introduction

The study is designed as a prospective, controlled, double-blind, multicentre, randomised equivalence clinical trial comparing clonidine and midazolam as intravenous sedative agents in critically ill children. Study treatments are manufactured and supplied by SCM Pharma to enable provision of double blind study treatments. Pre-randomised, sequentially numbered, treatment packs will be securely stored within each participating PICU. Once consent is obtained, patients will be allocated the next available treatment pack in the sequence appropriate for their weight (7.3). Staff on PICU will prepare the medications for infusion on the Unit upon completion of all pre-trial administrative procedures. The patient will be loaded with morphine and trial drug solution according to the scheme in appendix C.

7.2 Packaging, Labelling, Storage and Stability

Blinded vials will be produced by SCM Pharma, Northumberland, who will supply labelled and blinded treatment kits according to randomisation lists provided by the MCRN CTU. These will be QP released by SCM Pharma.

Ampoules of trial treatment will be 5ml in volume and the concentrations of trial treatments permit blinding of the two study treatments as it results in identical volumes being required for enrolled patients. The addition of identical labelling, packaging and containers enables the study treatments to be blinded. The ampoules of study treatment will be received and stored by the pharmacy department at each centre and stored at 2^{o}C to 30^{o}C. Supplies will be released to each PICU for storage to ensure that there are always surplus supplies available on the Unit to enable a participant to be enrolled onto the study at any time (therefore not relying on a 24 hour pharmacy). On PICU, supplies will be stored in a locked cabinet also at 2^{o}C to 30^{o}C. The cabinet will contain a maximum/minimum thermometer to monitor storage conditions. This should be checked daily and the results recorded on the log provided. Should the temperature fall outside of range the site will contact the CTU who will advise on the course of action. In the event a discrepancy is detected out of hours, the kits should not be used until support is available.

The trial treatment has a shelf life of 12 months. The Trial Coordinator will ensure that all sites have sufficient supplies, that shelf life is increased where necessary, that destruction of those supplies where shelf life has expired is arranged and resupply occurs where appropriate. Clinical trial supplies can only be delivered to investigator sites once the site has been initiated. This can only be completed once full ethics and regulatory approval has been granted. This must be confirmed by the Trial Co-ordinator acting on behalf of the study sponsor.

7.3 Preparation and administration of Trial Treatments

Each patient treatment package will contain sufficient ampoules for 7 days of study treatment.

The PICU nurse will prepare the study drug for infusion (section 7.4) according to which weight group the patient falls into:

a) <10kg (yellow pack)
b) 10-25kg (blue pack)
c) >25kg-50kg (pink pack)

Syringes will be prepared for infusion as required for each patient. A 21 gauge (0.81mm outer diameter) needle or smaller should be used to draw out the treatment from the vial to ensure that the extractable volume is adequate.

If it is not possible to weigh patient, please estimate using the formula/method that is routinely used clinically on the Unit and record an actual weight as soon as it is possible to weigh the child (if this possible).

The table below illustrates the preparation of trial treatment for infusion, rate range of infusion, the loading dose, the maintenance rate and incremental steps to be applied for each weight group for two trial treatments. Additional details can be found in Appendix C.

Table 1. Trial treatment regimen according to weight

Treatment schedule	**A**	**B**	**C**
Childs weight (kg)	**<10kg**	**10kg – 25kg**	**>25kg – 50kg**
Preparation of trial treatment for infusion	5ml trial treatment in 50ml 5% dextrose	6.25ml trial treatment in 50ml of 5% dextrose	25ml trial treatment in 50ml of 5% dextrose
Rate range of infusion	0.05ml/kg/hr to 0.2ml/kg/hr	0.04ml/kg/hr to 0.16ml/kg/hr	0.01 ml/kg/hr to 0.04ml/kg/hr
Loading dose (First hour of trial treatment)	0.2ml/kg over 1 hour	0.16ml/kg over 1 hour	0.04ml/kg over 1 hour
Maintenance rate (hour two of trial treatment)	0.1ml/kg/hr	0.08ml/kg/hr	0.02ml/kg/hr
Incremental steps (from hour three; reviewed hourly and adjusted according to COMFORT score)	Increase in steps of 0.05ml/kg/hr	Increase in steps of 0.04ml/kg/hr	Increase in steps of 0.01ml/kg/hr

Note: If infusion pump does not allow measure please follow the advice below:

- **If measure is more than or equal to 0.5 of the increment then doses should be rounded up to the 0.1ml above.**
  If measure is less than 0.5 of the increment then measure should be rounded down to the 0.1ml below.

NB. Trial treatment (Clonidine or Midazolam) and morphine should be infused on the same line which must be dedicated to the administration of trial treatment and morphine. Morphine and trial treatment are compatible and should be infused as close as possible to the cannula to avoid flushes and to assure that small adjustments of the infusion speed are delivered in time to the patient.

7.4 Formulation and Dosage of Trial Treatments

7.4.1 Clonidine

Ampoules of clonidine will be 5ml in volume and contain a concentration of 150 micrograms/ml of clonidine. The table below illustrates the dosage of clonidine to be administered to each weight group and incremental dose increases according to the treatment regimen based upon using these ampoules. Additional details can be found in Appendix C.

Table 2. Clonidine treatment regimen according to weight

Treatment schedule	**A**	**B**	**C**
Childs weight (kg)	**<10kg**	**10kg – 25kg**	**>25kg – 50kg**
Preparation for infusion	5ml clonidine in 50ml 5% dextrose *(15 micrograms/ml)*	6.25ml clonidine in 50ml of 5% dextrose *(18.75 micrograms/ml)*	25ml clonidine in 50ml of 5% dextrose *(75 micrograms/ml)*
Rate range of infusion	0.05ml/kg/hr to 0.2ml/kg/hr *(0.75micrograms/kg/hr to 3 micrograms/kg/hr)*	0.04ml/kg/hr to 0.16ml/kg/hr *(0.75micrograms/kg/hr to 3micrograms/kg/hr)*	0.01 ml/kg/hr to 0.04ml/kg/hr *(0.75micrograms/kg/hr to 3micrograms/kg/hr)*
Loading dose (First hour of trial treatment)	0.2ml/kg over 1 hour *(3micrograms/kg/hr)*	0.16ml/kg over 1 hour *(3micrograms/kg/hr)*	0.04ml/kg over 1 hour *(3micrograms/kg/hr)*
Maintenance rate (hour two of trial treatment)	0.1ml/kg/hr *(1.5micrograms/kg/hr)*	0.08ml/kg/hr *(1.5micrograms/kg/hr)*	0.02ml/kg/hr *(1.5micrograms/kg/hr)*
Incremental steps (from hour three; reviewed hourly and adjusted according to COMFORT score)	Increase in steps of 0.05ml/kg/hr	Increase in steps of 0.04ml/kg/hr	Increase in steps of 0.01ml/kg/hr

Note: If infusion pump does not allow measure please follow the advice below:

- **If measure is more than or equal to 0.5 of the increment then doses should be rounded up to the 0.1ml above.**
  If measure is less than 0.5 of the increment then measure should be rounded down to the 0.1ml below.

7.4.2 Midazolam

Ampoules of midazolam will be 5ml in volume and contain a concentration of 10 milligrams/ml of midazolam. The table below illustrates the dosage of midazolam to be administered to each weight group and incremental dose increases according to the treatment regimen based upon using these ampoules. Additional details can be found in Appendix C.

Table 3. Midazolam treatment regimen according to weight

Treatment schedule	**A**	**B**	**C**
Childs weight (kg)	**<10kg**	**10kg – 25kg**	**>25kg – 50kg**
Preparation for infusion	5ml midazolam in 50 ml 5% dextrose *(1 mg/ml)*	6.25ml midazolam in 50ml 5% dextrose *(1.25mg/ml)*	25ml midazolam in 50ml 5% dextrose *(5mg/ml)*
Rate range of infusion	0.05ml/kg/hr to 0.2ml/kg/hr *(50micrograms/kg/hr to 200 micrograms/kg/hr)*	0.04ml/kg/hr to 0.16ml/kg/hr *(50micrograms/kg/hr to 200 micrograms/kg/hr)*	0.01ml/kg/hr to 0.04ml/kg/hr *(50micrograms/kg/hr to 200 micrograms/kg/hr)*
Loading dose (First hour of trial treatment)	0.2ml/kg over 1 hour *(200micrograms/kg/hr)*	0.16ml/kg over 1 hour *(200micrograms/kg/hr)*	0.04ml/kg over 1 hour *(200micrograms/kg/hr)*
Maintenance rate (hour two of trial treatment)	0.1ml/kg/hr *(100micrograms/kg/hr)*	0.08ml/kg/hr *(100micrograms/kg/hr)*	0.02ml/kg/hr *(100micrograms/kg/hr)*
Incremental steps (from hour three; reviewed hourly and adjusted according to COMFORT score)	Increase in steps of 0.05ml/kg/hr	Increase in steps of 0.04ml/kg/hr	Increase in steps of 0.01ml/kg/hr

Note: If infusion pump does not allow measure please follow the advice below:

- **If measure is more than or equal to 0.5 of the increment then doses should be rounded up to the 0.1ml above.**
- **If measure is less than 0.5 of the increment then measure should be rounded down to the 0.1ml below.**

7.5 Morphine Sulphate

All patients will be prescribed morphine sulphate as per standard clinical practice in the PICU when administering sedation. This will be dispensed and administered as per clinical protocol for the given unit. Irrespective of previous therapy, a loading dose of 100 micrograms/kg morphine will be given over 15 minutes, which will be followed immediately by the commencement of the blinded study drug. This will be followed by an infusion of 20 micrograms/kg/h. All previously administered sedation drugs will be stopped at the commencement of the loading of morphine, leaving morphine and the study drug as the sole sedation/analgesia medication.

7.6 Unblinding

7.6.1 Unblinding of Individual Participants During Trial Conduct

Breaking the statistical blind should be considered only when knowledge of the treatment assignment is deemed essential for the participant's care by the participant's physician or a regulatory body; In general, unblinding of participants during conduct of the clinical trial is not allowed unless there are compelling medical or safety reasons to do so.
N.B. If simply ceasing study treatment is a viable option for the patient's care, it should not be necessary for unblinding to occur.

7.6.1.1 Procedure

a. The decision to unblind a single case should be made when knowledge of an individuals allocated treatment is essential to:
    i. Enable treatment of severe adverse event/s, or
    ii. Enable administration of another therapy that is contraindicated by the trial treatment
b. *Where possible* (during office hours), consent for individual unblinding should be made via the trial coordinator at MCRN CTU who will seek agreement of Chief Investigator (Prof A Wolf)
c. Unblinding codes will be held on the PICU in pressure sealed envelopes. (Unblinding envelopes will be checked to ensure that they have not been tampered with; at monitoring visits and at more regular intervals where deemed appropriate).
d. Individual patient only to be unblinded and the following is to be documented:
    i. Date information needed
    ii. Detailed reason for unblinding
    iii. Identity of recipients of the unblinding information
e. The local investigator will ensure all necessary CRFs to time of unblinding are completed and submitted to MCRN CTU (if possible, completed *before* unblinding is performed)
f. All instances of unblinding should be recorded and reported in writing to the MCRN CTU by the local investigator, including the identity of all recipients of the unblinding information.
g. Allocation should not routinely be revealed to MCRN CTU personnel

7.6.2 Accidental Unblinding

All instances of inadvertent unblinding should be recorded and reported in writing to the MCRN CTU by the local investigator. Reports to include:

a. Date of unblinding
b. Detailed explanation of circumstances

c. Recipients of the unblinding information
d. Action to prevent further occurrence
e. Allocation should not be routinely revealed to MCRN CTU personnel

7.6.3 At Trial Closure

The end of the trial will be considered as the date of the final database lock. In the event that the trial is closed prematurely by the Trial Steering Committee, on the recommendation of the Data Monitoring Committee, for reasons such as clear differences between safety of trial treatments, the end of the trial will still be considered as the date of the final database lock. Upon trial closure the pharmacy at each participating site will return unblinding codes without breaking the seals to reveal allocation codes, to the MCRN CTU. MCRN CTU will notify local investigators in writing of unblinding information for patients under their care. A copy of this notification should be placed in the medical records and a copy retained in the site file. It is the responsibility of the local investigator to notify trial participants of their allocated treatment.

7.7 Accountability Procedures for Study Treatment/s

The ampoules of study drugs will be received by the pharmacy department and released for storage on the PICU where they will be stored securely. PICU will maintain a log of ampoules utilised when the drug is prepared for infusion. The pharmacy will then take receipt of any ampoules which were surplus to requirements for a patient (i.e. where study treatment duration was less than 7 days) and complete a record of accountability. Study drug will then be destroyed.
All trial drugs will be kept under locked key at 2^{o}C to 30^{o}C.

7.8 Assessment of Compliance with Study Treatment/s

Allocated trial treatments will be administered IV by PICU personnel. All administrations are recorded on drug prescription sheets and infusion charts documenting rate of infusion are maintained.

7.9 Concomitant Medications/Treatments

7.9.1 Medications Permitted

Randomised patients will be given morphine in addition to the allocated trial treatment. Any additional sedation or analgesia administered alongside the allocated trial medication should be documented on the CRF. The following medications are permitted:

Supplementary analgesia (general care): paracetamol, ibuprofen or diclofenac as per usual clinical practice on the PICU

Supplementary analgesia for specific procedures*: regional anaesthetic blockade with local anaesthesia and opioids, additional IV morphine, IV fentanyl, IV alfentanil, IV remifentanil

Supplementary anaesthesia for specific procedures*: propofol, ketamine, thiopentone sevoflurane, isoflurane, desflurane, midazolam, diazepam, lorazepam, chlorpromazine, haloperidol, promethazine.

Muscle relaxant drugs are permissible only if used specifically for procedures/reintubation. When paralysed, COMFORT score cannot be recorded therefore continue sedation as per trial protocol (if possible and appropriate) and recommence recording COMFORT score data when patient is no longer paralysed. When COMFORT score cannot be recorded, this must be documented as missing data in the CRF and a reason must be given.

*Invasive procedures such as change of endotracheal tube, insertion of an invasive monitoring line or surgical procedure. If any muscle relaxant drugs are used, this should be documented on the CRF.

Recommended drugs and doses for rescue doses
The following doses are provided for guidance only and rescue doses may be decided by individual units according to their local unit policy should they wish to.

Analgesia drugs
Morphine IV 0.1-0.3 mg/kg
Fentanyl IV 2 -10mcg/kg
Ketamine IV 1-2mg/kg

Sedation drugs
Midazolam IV 0.1-0.3mg/kg
Lorazepam IV 0.05 – 0.1mg/kg
Diazepam IV 0.1-0.3mg/kg
Chlorpromazine IV 0.5mg/kg
Haloperidol IV 0.15mg/kg
Promethazine IV 0.5mg/kg

Paralysis drugs
Vecuronium IV 0.15mg/kg
Pancuronioum IV 0.1mg/kg
Atracurium IV 0.1mg/kg
Rocuronium IV 0.4mg/kg

7.9.2 Medications Not Permitted/ Precautions Required

Beta Blockers: Children receiving beta blocker drugs at time of screening will be excluded from trial entry.
Due to potential effects on heart rate (bradycardia) and blood pressure (hypotension), patients requiring beta blockade during the trial will be withdrawn from the study.

Enteral sedation (e.g. chloral hydrate): Not permitted.

7.9.3 Data on Concomitant Medication

Doses and names of analgesia and sedation therapy will be recorded at baseline. Any supplementary analgesia, sedation or muscle relaxants required during trial treatment and an indication of whether concomitant medications were required to treat withdrawal symptoms will be documented on the CRF.When reporting a Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) all concomitant medication will require to be recorded on the CRF.

7.10 Dose Modifications

7.10.1 Dose Increases

Dose modification is the essential variable in this study and all increases are made based upon the hourly COMFORT score recorded. Additional details can be found in Appendix C. Infusion rates of the allocated treatment will be adjusted in increments according to the scheme set out in Appendix C. Evaluation of sedation will be made using the COMFORT score[44,45] (Appendix A) on an hourly basis by nurses who have been trained with the technique. If the patient has a COMFORT score of above 26 indicating that sedation is inadequate, the bedside nurse should evaluate the patient for both pain and their conscious level. If the patient is judged to be in pain then the morphine should be increased by 10micrograms/kg/hr (up to a maximum of 60 micrograms/kg/hr). If the patient is judged to have a lack of sedation then the trial drug should be increased by the designated amount (please see Table 1, section 7.3). Only one incremental change can occur per documented COMFORT score for the trial sedation or morphine. There can be more than one incremental change per hour provided this is accompanied by a documented COMFORT score. If the maximum allowed dose of morphine and trial sedation is reached and the child is still judged to be inadequately sedated, this will be recorded as a treatment failure and sedation will then be transferred to alternative sedation according to the individual units treatment policy. A treatment failure will also be recorded if 3 'events'* where rescue medication are needed to re-establish sedation or pain control occur within one 12 hour period. This does not include the administration of concomitant medications for procedures. During the study additional care procedures may be managed with supplemental fentanyl, Propofol, thiopentone, diazepam, additional morphine or midazolam according to the usual unit policy.

If sedation is stopped before 1 week due to recovery, then all drugs should be stopped abruptly and any withdrawal or analgesia issues treated as they emerge. If there are ongoing analgesia requirements these will need to be treated appropriately with analgesic drugs and recorded in the trial CRF.

If at the end of the trial period (maximum of 1 week) sedation needs to be continued then an alternative is to be used according to the unit policy.

*an 'event' is described as a point when control of sedation is deemed to be acutely lost requiring immediate intervention. The intervention can involve more than one drug given over a short period of time to establish rapid control (within approximately a 30 minute window to allow safe titration if necessary).

Scheme for adjustment of Infusions

1. Load and start infusions
2. COMFORT score hourly (target $\leq 26 \geq 17$)
3. Increase or decrease study medication infusion based on COMFORT score as per schematic diagram (pg 11) and using the incremental changes described above. Protocol dictates that the decision to increase or decrease study medication or morphine should be made hourly*, according to the COMFORT score. Nurses at the bedside will need to assess the patient for pain and their conscious level to determine whether morphine or trial sedation should be increased or decreased.
4. If sedation remains inadequate after an hour of maximum study drug and maximum morphine (60micrograms/kg/hr), treatment failure will have been deemed to have occurred. Switch to alternate sedation as per unit protocol. Continue with measurements of COMFORT and blood pressure described above.

5. If sedation is re-established and COMFORT score falls to below 17 and remains below 17 for two hours (two subsequent COMFORT scores), reduce morphine or trial sedation incrementally as clinically indicated (according to subsequent COMFORT scores and bedside evaluation of pain or sedation component of disturbance) down to a minimum of 20micrograms/kg/hr for morphine or to the minimum infusion rate for the weight group for the child.
6. If during study a painful procedure needs to be undertaken such as physiotherapy, chest drain placement, line placement or other intervention that is likely to be associated with a short period of increased discomfort necessitating additional anaesthesia or analgesia this can be provided. Trial medication should remain at the same infusion rate throughout this period until the effects of other drugs have worn off. Drugs used may include: Propofol, volatile anaesthetic agents, thiopentone ketamine, fentanyl morphine or midazolam. Careful documentation of these concomitant medications will be made and evaluations as per the study will continue. Muscle relaxants are also permissible for procedures where this is deemed necessary by the independent clinician. Additionally if there is a sudden loss of sedation/ analgesia control associated with “cares” or other minor events (turning the patient) that is deemed to require urgent treatment, it is permissible to give sedation/ analgesia from the list above. The details should be logged as a concomitant medication and the event recorded. The trial drug should continue to be delivered according to hourly summary COMFORT scores. Similarly if increased sedation is required for procedures such as an MRI or CT scan this should be treated the same way as for the procedures such as chest drain placement

* If clinical judgement indicates that it is necessary to increase or decrease study medication before the hour has ended then adjustments may be made to ensure the comfort and safety of patients. This activity should be recorded on the CRF and a COMFORT score recorded at that timepoint where possible.

7.10.2 Dose Reductions

Dose modification is the essential variable in this study and all details on increases are shown in appendix C. The dose reductions are all based on regular hourly COMFORT scores. If the COMFORT score falls to below 17 and is sustained for two hours (two subsequent COMFORT scores), reduce morphine or trial sedation incrementally as clinically indicated (according to subsequent COMFORT scores) down to a minimum of 20micrograms/kg/hr for morphine or the minimum infusion rate for trial sedation for the appropriate weight group. Incremental reductions for morphine are 10micrograms/kg/hr and incremental reductions of trial sedation should be made as detailed in the schedule on the following page (Table 4). Only one incremental reduction should be made per COMFORT score. If, after a reduction in trial medication, the COMFORT score increases to 17 or above then the trial medication should remain at that infusion rate until further assessment of COMFORT score at the next hourly interval which will dictate whether a change in infusion rate is required.

If the minimum trial infusion rate and the morphine infusion rate of 20 micrograms/kg/hr is administered and the COMFORT score of the child is still below 17, then if there are no analgesic requirements, the morphine can be further decreased by an increment of 10micrograms/kg/hr to 10micrograms/kg/hr. If at the subsequent COMFORT score, the COMFORT score is still below 17, the morphine can be stopped (providing there are no analgesic requirements). If at the subsequent COMFORT score, the COMFORT score is still below 17, the trial sedation can be temporarily stopped.

Table 4. Incremental reduction rates for trial medication infusion

Treatment schedule	**A**	**B**	**C**
Childs weight (kg)	**<10kg**	**10kg – 25kg**	**>25kg-50kg**
Incremental steps of infusion rate reduction (reviewed hourly and applied if COMFORT score below 17 and morphine infusion at 20micrograms/kg/hr)	Reduce in steps of 0.05ml/kg/hr	Reduce in steps of 0.04ml/kg/hr	Reduce in steps of 0.01ml/kg/hr

In the event of a serious adverse event the drug will only be unblinded if the criteria outlined in section 7.6 are fulfilled.

7.10.3 Withdrawal from Trial Intervention

Trial treatment may be withdrawn if criteria in section 5.3.2 are fulfilled.

7.10.3.1 Treatment of Withdrawal Symptoms

Following cessation of trial treatment, withdrawal symptoms should be treated according to local Unit policy and documented in the CRF.

7.11 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally patients should not be recruited into other trials. Individuals that have participated in a trial testing a medicinal product within one month preceding the study will be ineligible for the study. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the SLEEPS trial this must first be discussed with the coordinating centre (MCRN CTU) who will contact the chief investigator (Prof A Wolf).

8 ASSESSMENTS AND PROCEDURES

8.1 Schedule for Follow-up

Randomisation and commencement of trial treatment must occur within 24 hours of consent being taken. The minimum anticipated trial treatment period is 12 hours (as per eligibility criteria) and the maximum duration of the trial treatment is 1 week. Patients requiring continued sedation and analgesia following seven days of allocated trial medication will be changed from the blinded drug regimen according to individual unit policy in accord with established clinical practice of "drug cycling" to avoid tolerance[46]. These patients, and those who cease trial medication within 7 days of it commencing, will continue to be followed up after stopping the trial therapy until hospital discharge to look for haemodynamic disturbance and withdrawal phenomena (Appendix B). Haemodynamic surveillance will consist of hourly recording of heart rate and blood pressure while still on the PICU after cessation of sedative drugs for a period of 24 hours. This primarily to look for rebound hypertension or tachycardia after stopping the study drugs.

Patients who have been discharged to the ward in the 24 hours after cessation of trial allocated therapy will receive 4 hourly observations only (heart rate and blood pressure). Heart rate and blood pressure will then be assessed 6 hourly for a maximum of 5 days in all patients or until patient is discharged, whichever is soonest. Assessment of withdrawal symptoms will take place 4 hourly for the first 24 hours following treatment cessation and once daily on ward for a maximum of 5 days or until patient is discharged, whichever is soonest. When a patient is discharged to a ward at the hospital where they have been in PICU or to a ward at a hospital other than the one where they have been in PICU (i.e. to a District General Hospital), the research nurse will make a daily phone call to the ward. The research nurse will ask for details of heart rate, blood pressure and withdrawal symptoms and will record them in the CRF.

14 days following treatment cessation, the research nurse will contact the ward (if the patient has not been discharged from hospital) or the patient or the parent/guardian of the patient (if they have been discharged) to enquire as to whether there have been any adverse events in the last 9 days. If there have been any adverse reactions or serious adverse events (please see section 10.1 for definitions), these will be recorded in the CRF.

8.2 Procedures for assessing Equivalence

1. **COMFORT score**

   The COMFORT score is a behavioural, unobtrusive method of measuring distress in unconscious and ventilated infants, children and adolescents. The scale consists of 8 indicators that are scored between 1 and 5 and are based upon the behaviours exhibited by the patient. Patients will be observed over the previous hour and the total score is derived by adding the scores of each indicator. Total scores can range between 8-40 and a score of 17-26 is considered to indicate adequate sedation and pain control. The COMFORT score will dictate whether increases or decreases in study medication and morphine occur.

   (See Appendix A for COMFORT score and guide for using the assessment)

   The COMFORT score will be assessed once an hour during administration of trial treatment but if clinician judgement indicates that it is necessary to increase or decrease study medication before the hour has ended, a COMFORT score should be recorded and adjustments made to ensure the comfort and safety of patients.

If a procedure/intervention occurs in the period between two COMFORT score assessments then the observations relating to the procedure/intervention should be discounted from the COMFORT score assessment.

Once trial treatment has ceased the COMFORT score should continue to be measured hourly until the patient is fully awake (determined by a score of a 4 on the alertness category of the COMFORT score sustained for 2 hours). If the child is no longer ventilated, the only COMFORT score category that needs to be completed is 'Alertness'. If sedation is still required following cessation of the trial treatment the COMFORT score should continue to be measured hourly until the child is stable on the new sedative(s). The child is considered to be stable on the new sedative once a COMFORT score of 17-26 has been sustained for two hours.

8.3 Procedures for Assessing Safety

1. **Heart Rate**
   Heart Rate will be recorded using standard PICU equipment; hourly during administration of trial therapy, hourly for 24 hours following cessation of trial therapy if on PICU or 4 hourly if transferred to the ward. Following this, heart rate will be recorded 6 hourly for 5 days following treatment cessation or until discharge, whichever occurs soonest.
2. **Blood pressure**
   Blood pressure will be recorded by standard PICU equipment either invasively through an arterial cannula or non invasively with a standard sphygmanometer.
   Blood pressure will be recorded hourly during administration of trial therapy, hourly for 24 hours following cessation of trial therapy if on PICU or 4 hourly if transferred to the ward. Following this, blood pressure will be recorded 6 hourly for 5 days following treatment cessation or until discharge, whichever occurs soonest.
3. **AE assessments**
   Any untoward and unintended response that occurs in a participant in the trial that is suspected to be related to any dose administered of either Midazolam or Clonidine will be considered to be a suspected adverse reaction and must be reported.
   All adverse reactions suspected to be related to either of the trial treatments should be reported on the Adverse Reaction Case Report Form, however for ease of completion a list of known adverse reactions will be provided on this CRF; the list will comprise of the following:
   - Hypotension that requires intervention
   - Bradycardia that requires intervention
   - Hypertension following cessation of trial treatment

   Non-serious adverse events do not need to be reported.

   Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that fulfil the criteria of a serious event (see section 10.1) must be reported using the Serious Adverse Event CRF, regardless of whether they are suspected to be related to the administration of Midazolam or Clonidine.

   Signs and symptoms will be graded and reported as; mild symptoms (score 1); moderate symptoms (score 2) and severe symptoms (score 3). Seriousness and causality will also be assessed by the reporting researcher (see section 10). All Adverse Reactions, Serious Adverse Events, Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions will be recorded from

randomisation until 14 days following cessation of trial treatment. Please see section 10 for further details of reporting procedures and requirements.

Adverse events assessments should take place until 14 days following treatment cessation.

4. **Withdrawal symptoms**
   This assessment is based on 11 descriptors that have been agreed as a basis for abnormal behaviour derived by the Paediatric Intensive Care Society Study Group on Sedation (PICSSG)[47] (Appendix B). If any of the symptoms are occurring at an assessment timepoint then they will be logged in the chart and rated as mild, moderate or severe. If there is any abnormal behaviour observed that is not listed then this should be specified in the "Other" row. Assessment of withdrawal symptoms will begin when sedation ceases. They will be assessed 4 hourly for the first 24 hours following treatment cessation and following this once daily on the ward for a maximum of 5 days or until discharge, whichever is soonest.
5. **Fluid balance**
   A total of fluid in and out for each 24 hour period will be recorded as per in-house fluid balance regimens. Total input will include all maintenance fluids, blood products, infusion pumps etc and the fluid out measurement will include all measurable secretions (urine, net nasogastric losses, drains, blood loss etc). Fluid balance will be recorded daily during trial treatment.
6. **Clinical Laboratory**
   Blood biochemistry: Sodium, potassium, chloride, urea, creatinine, bilirubin, ALT/AST and alkaline phosphatase will be recorded from routine daily blood biochemistry, if these measurements are available. Blood biochemistry will be recorded from randomisation until trial treatment ceases. If routine blood biochemistry is being continued following treatment cessation then these values will be recorded for study purposes up until a maximum of 5 days following treatment cessation or until discharge, whichever is soonest.
   Urinalysis: Urea and creatinine will be assessed from a 5ml sample of urine. Urinalysis will be carried out daily once treatment has been administered for 24 hours, throughout treatment administration and following treatment where routine samples are analysed and the relevant data is available.
7. **Ventilated days**
   The number of ventilated days will be recorded for each patient.

Table 5. Schedule of Study Procedures

Procedures		Enrolment and baseline*		T+(DAYS) Maximum Number of Treatment Days							Follow-up Days (F)						Premature Discontinuation
			T0	1	2	3	4	5	6	7	F1	F2	F3	F4	F5	F14	
Signed Informed Consent*		X															
Randomisation*			X														
Verify consent/assent (as appropriate when sedation ceases)				(X)	(X)	(X)	(X)	(X)	(X)	(X)							
Assessment of Eligibility Criteria		X															
Review of Medical History		X															
Review of Concomitant Medications		X		X	X	X	X	X	X	X	X	X	X	X	X		X
Study Intervention**			X	X	X	X	X	X	X	X							
COMFORT Score[1]		X		X	X	X	X	X	X	X	X						
Blood Pressure & Heart Rate[2]		X		X	X	X	X	X	X	X	X	X	X	X	X		(X)
Fluid Balance[3]				X	X	X	X	X	X	X							(X)
Withdrawal Symptoms[4]				(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	X	X	X	X		(X)
Assessment of Adverse Events				X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Clinical Laboratory[5]	Chemistry	X		(X)	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	(X)	(X)		(X)
	Urinalysis			(X)	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	(X)	(X)		(X)
PK/PD and phthalate Study (limited number of centres participating in blood and urine sampling for PK/PD and phthalate substudy but only Bristol taking samples for urinary VMA and cardiac function for PK/PD study)	Blood sampling[6]			X	X	X	X	X	X	X							
	Urine sampling[7]			X	X	X	X	X	X	X							
	Urinary VMA[8]			X	X	X	X	X	X	X							
	Cardiac Function[9]			X	X	X	X	X	X	X							

(X) – As indicated/appropriate
*Should take place within 120 hours of PICU/ICU admission. Trial procedures should be done before administration of study intervention
**Proceed to follow-up (Day F1) upon cessation of trial therapy
[1]COMFORT score recorded hourly during infusion of trial therapy. Following cessation of trial therapy COMFORT score to be recorded until patient is fully awake (determined by a score of 4 on the alertness scale of the COMFORT score).
[2]Blood Pressure & Heart Rate recorded hourly during administration of trial therapy and for 24 hours afterwards on PICU or 4 hourly on ward, thereafter recorded 6 hourly for 5 days or until discharge – whichever is soonest
[3]Recording of intravenous and enteral intake, urine output, presence/absence of ileus, opening of bowels and toleration of feeds. Fluid balance is only required during trial treatment.
[4]Assessment of withdrawal symptoms, commencing when sedation ceases; 4 hourly in PICU for 24 hours and following this once daily on ward for a maximum of 5 days or until discharge – whichever is soonest
[5]Routine daily blood biochemistry outwith the trial: - Sodium, potassium, chloride, urea, creatinine, bilirubin, ALT/AST and alkaline phosphatase. Urinalysis – urea & creatinine. Urine will be collected for 24 hours and volume will be recorded. Approximately 5ml will be required for urinalysis (urea and creatinine at all sites) and 10ml urine for urinary VMA at Bristol only.

[6]Daily for duration of sedation infusion. Blood volume 2ml per kg weight of the child (**maximum** 20ml) In the subset analysis blood from the routine 6am test will be set aside for measurement of cortisol (50uL), gamma glutamyl transpeptidase and alkaline phosphatase.
[7] Daily. Sample to assess this taken from 24 hour collection of urine described in no.5 above.
[8] Daily. Sample to assess this taken from 24 hour collection of urine described in no. 5 above.
[9]Cardiac output (to include venous saturation, lactate, acidosis) and systemic vascular resistance index measured directly on a daily basis using velocimetry with the ICON non invasive cardiac output monitor (This commercially available device consists of an array of 3 ECG stickers which measures cardiac output using the first and second differentials of thoracic impedance with time).

8.4 Other Assessments

8.4.1 Health Economics

An economic evaluation will be integrated into the trial design. Data will be collected on the health service resources used in the treatment of each child during the time horizon covered by the randomised controlled trial. Data collection forms will record the duration and intensity of care provided to each child, based on standard criteria for level of care, as well as complications experienced. Details of the resources associated with salient clinical events will be recorded. Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. A *per diem* cost for each level of paediatric care will be calculated by the health economics researcher from detailed questionnaires completed by NHS finance departments, giving cost data and apportioning these to different categories of patient using a 'top-down' methodology. Each trial participating centre will be visited to ensure consistency in cost apportionments. The unit costs of clinical events that are unique to this trial will be derived from the hospital accounts of the trial participating centres, although primary research that uses established accounting methods may also be required.

An incremental cost-effectiveness analysis will be performed. In the baseline analysis, the economic evaluation will be expressed as the incremental cost per additional case of adequate sedation. Given the methodological limitations surrounding preference-based outcomes measurement in young children[48], outcomes will not be expressed in terms of preference-based metrics, such as the quality-adjusted life year. We shall use non-parametric bootstrap estimation to derive 95% confidence intervals for mean cost differences between the trial groups and to calculate 95% confidence intervals for incremental cost effectiveness ratios. A series of simple and probabilistic sensitivity analyses will be undertaken to explore the implications of uncertainty on the incremental cost-effectiveness ratios and to consider the broader issue of the generalisability of the study results. Sub-group analysis will be performed in order to assess the heterogeneity of the cost-effectiveness results across age, diagnostic and severity sub-groups. In addition, cost-effectiveness acceptability curves will be constructed using the net benefits approach.

The planned economic evaluation will conform to nationally agreed design and reporting guidelines[49]. It will be conducted from a health service perspective and will incorporate detailed resource use and clinical effectiveness data from all participants recruited into the trial. All unit costs employed will follow recent guidelines on costing health care services as part of economic evaluation[50,51]. The calculation of these costs will be underpinned by the concept of opportunity cost. The proposed analytical strategy will follow the recent requirements stipulated by decision-making bodies[49].

8.5 Substudy: Pharmacokinetic (PK)-Pharmacodynamic (PD) Studies

Parents of children at selected centres will be approached for consent to a more detailed pharmacometric study to examine the relationship between sedative drug dosing and drug effects and selected physiological and biochemical assessments to determine relative effects of the sedative agents on organ function. These studies will continue for a maximum of 1 week or until the patient no longer requires sedation.

8.5.1 Pharmacokinetic Measurements

Measurement of plasma concentrations of clonidine, midazolam and morphine using High Performance Liquid Chromatography with Mass Spectrometry (LC-MS) will be taken to determine pharmacokinetic parameter values and to assess the progression of pharmacokinetic tolerance. "Sparse sampling techniques" will be used to limit blood sampling and comply with current ethical limitations on blood volumes withdrawn for analysis in children. These measurements will be made by the Anaesthesia Research Group at the Peninsula Medical School, Plymouth which has considerable collaborative experience in the pharmacokinetics of sedative agents in PICU. These data will help to define adequate blood concentrations associated with clonidine and midazolam sedation that can drive drug administration regimens.

8.5.2 Pharmacokinetic and Pharmacodynamic Study Design

8.5.2.1 Pharmacokinetics (PK)

Existing PK data[52,53] will be used to construct an informative block randomised blood sampling scheme[54] that will be suitable for both cohorts (to maintain blinding). Periodically throughout the course of the 2 year study, the sampling scheme will be revised and optimised based on the PK data accrued thus far. This ensures that data continues to be collected at kinetically informative times. Total blood sampling for each child (recruited to either the PK-PD substudy and/or the TK-TD substudy study) will be limited to 2ml per Kg or 20ml, whichever is the lesser amount (details of TK-TD study given below).

8.5.2.2 Pharmacodynamics (PD)

The pharmacodynamic marker of sedation will primarily be the COMFORT score, but pharmacodynamic models of other drug concentration-dependent physiological parameters, e.g. blood pressure, will be examined.

8.5.2.3 PK-PD Data analysis

Data will be analysed using nonlinear mixed-effects modelling (NONMEM software[55] which is particularly suited to analysing data from paediatric studies where there may be sparse and unbalanced PK data collection[56]. The following covariate data will be obtained for each individual: height, weight, body surface area, age, and disease status. Concomitant and recent drug therapy will be recorded. In addition, measurements of cardiovascular performance, stress response and organ function (detailed below) will be recorded as time-varying covariates. Establishing relevant covariate-pharmacokinetic/dynamic parameter relationships will be the main objective of this analysis as it explains parameter variability within a study population and, ultimately, facilitates dose adjustment decisions.

8.5.2.4 PK Study Sample Size

While there is no straightforward sample-size calculation for population PK analyses, simulation studies have demonstrated that a sample size of 100 participants is necessary for accurate and precise estimation of fixed and random effects parameters, where the interindividual variance is moderate[57,58]. Hence, we will study 100 patients in each cohort.
Assessment of benefits/side effects of the study drugs will be by measurement of all the physiological parameters listed below.

Cardiovascular measurements: clonidine may be associated with improved organ perfusion and cardiac output via reduced sympathetic outflow. We will measure: heart rate, blood pressure (hourly), venous oxygen saturation, blood lactate and acid base status (from routine blood gas analysis every 6 hours) and record inotropic requirements. Cardiac output

and systemic vascular resistance index will be measured directly on a daily basis using a commercially available non invasive technique using Oesophageal Doppler and analysis of pulse wave.
Stress responses: morning cortisol and urinary VMA will be used to assess the effects of clonidine on pituitary cortical and pituitary medullary responses.

Renal function: this will be assessed daily in terms of quality and output from recording daily urine output and paired plasma/urine creatinine and urea concentrations. Urine concentrations of gamma glutamyl transpeptidase and alkaline phosphatase, which have been shown to be sensitive markers of tubular function and renal integrity in intensive care patients[59] will also be measured daily.

Late complications: after 1 week the trial drugs will be discontinued. Further sedative management will be at the discretion of the clinician in charge of the unit. However the study will remain blinded so that later complications can be observed both in PICU and on the regular ward after discharge. Specific interest will focus on cardiovascular or behavioural changes associated with cessation of the study drug. Heart rate and blood pressure will be recorded 6 hourly for 7 days following cessation of the study drug. Withdrawal phenomena will be assessed according to standardised criteria currently being evaluated by PICSG. Withdrawal will be treated by administration of oral clonidine according to standardised unit protocol.

8.6 Substudy: Phthalate Toxicokinetic & Toxicodynamic Study

Parents of children at selected centres will be approached for consent for participation in a toxicokinetic substudy. This study will investigate whether children in UK intensive care units are being routinely exposed to potentially dangerous amounts of phthalate plasticiser, in the form of diethylhexylphthalate (DEHP). DEHP is added to polyvinylchloride (PVC) to soften the plastic and confer flexibility. It has been shown to leach from PVC medical devices (e.g. infusion bags, extension sets) into drug infusions ([59,60,61]). DEHP is an animal carcinogen, and a reproductive and developmental toxicant in animals and humans. ([62,63,64])

Data describing the kinetic profile of DEHP and DEHP metabolites are scarce and tend to be the result of a single investigation of one patient or volunteer ([65,66,67]). To obtain an accurate picture of the current potential for exposure to phthalate chemicals in PICU, and to establish whether younger patients (babies, infants) are more at risk than older children, there is a need to study multiple patients. Small numbers of measurements in many patients can yield statistically relevant results when data are analysed appropriately. Controlled toxicokinetic studies are not possible in children so risk assessment is increasingly utilising physiologically based toxicokinetic (PBTK) models.

8.6.1 Toxicokinetics (TK)

This section of the study will quantify DEHP metabolite concentrations in blood samples (arterial or venous) and urine samples collected before (on admission to establish baseline concentrations) and after cardiac surgery (cardiac surgery groups) and at the start (on admission), during and end of critical care (critical care groups).

Total blood sampling for each child (recruited to either the PK-PD substudy and/or the TK-TD substudy study) will be limited to 2ml per Kg or 20ml, whichever is the lesser amount.

Phthalate metabolite concentration in biological samples will be determined using High Performance Liquid Chromatography with Mass Spectrometry (LC-MS). The phthalate concentration data will be used to develop population toxicokinetic models of DEHP exposure. Blood and urine sample analysis and modelling will be performed by the Anaesthesia Research Group at the Peninsula Medical School (PMS), Plymouth. These data will be used to identify populations of greatest risk from DEHP exposure, and help determine 'dose' limits.

8.6.2 Toxicodynamics (TD)

The Anaesthesia Research Group at PMS will collaborate with their colleagues in the Environment and Human Health Research Group to investigate potential biomarkers of DEHP exposure. The Environment and Human Health Research Group are actively researching both biomarkers for exposure-response relationships and endocrine disrupting chemicals as marine pollutants ([68,69,70]). By incorporating potential biomarker data (such as testosterone or insulin-like factor 3 blood concentrations) ([71,72]) dynamics of phthalate exposure can be assessed and this would greatly strengthen risk assessment of phthalates in the critical care environment.

8.6.3 TK-TD Data analysis

Classic compartmental models and physiologically based toxicokinetic models will be evaluated using nonlinear mixed-effects modelling (NONMEM software). Attempts will be made to relate the extent of phthalate exposure to the patients' demographic data (age, body weight) and also to their individual critical care experience. That is, we hypothesise that patients whose medical care is of longer duration and/or involves greater exposure to plastics will demonstrate higher phthalate metabolite concentrations.

To allow this type of analysis, the duration and timing of critical care procedures and of biological sampling will be carefully recorded. Also recorded will be brand and type of infusion system used; brand, volume and concentration of lipid/TPN/drugs administered; and type and volume of administered blood products. The duration of cardiopulmonary bypass will be recorded for patients undergoing cardiac surgery. The duration of extra corporeal membrane oxygenation will be recorded for patients who receive this treatment.

8.7 Loss to Follow-up

If any of the trial patients are lost to follow up, contact will initially be attempted through the trial Research Nurses and the lead investigator at each Centre. If the lead investigator at the trial Centre is not the patient's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician.

8.8 Trial Closure

The end of the trial will be considered as the date of the final database lock, however the trial may be closed prematurely by the Trial Steering Committee, on the recommendation of the independent Data Monitoring Committee, for reasons such as clear differences between efficacy or safety of trial treatments

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full statistical analysis plan will be developed prior to the analysis of the trial. The analysis plan will be agreed by the Trial Steering Committee before being sent to the Independent Data Monitoring and Safety Monitoring Committee for comment and approval.

9.2 Method of Randomisation

Randomisation lists will be generated in STATA using simple block randomisation with random variable block length. Randomisation will be stratified by centre and weight.

The weight groups will be as follows:

a) < 10kg
b) 10-25kg
c) >25kg-50kg

9.3 Outcome Measures

9.3.1 Primary

The primary endpoint is adequate sedation defined as at least 80% of total evaluated time spent sedated within a COMFORT score range of 17 to 26.

9.3.2 Secondary

During study treatment phase

1. Percentage of time spent adequately sedated
2. Time to reach the maximum permitted dose of sedation
3. Time to reach the maximum permitted dose of morphine
4. Profile in rise of daily cumulative sedative infusion
5. Profile in rise of daily cumulative morphine infusion
6. Maximum permitted dose of sedative reached
7. Maximum permitted dose of morphine reached
8. Fall in blood pressure judged by clinician to require intervention
9. Increased inotropic support required in 1st 12 hours after randomisation
10. Supplementary analgesia required during sedation
11. Daily urine output
12. Treatment failure defined as inadequate sedation after one hour of maximum doses of sedative and morphine infusions (determined by a COMFORT score above 26) or treatment failure defined as three *'events' where rescue medication are needed to re-establish sedation or pain control occuring within any one 12 hour period during trial treatment
13. Blood biochemistry and urinalysis
14. Urinary concentration of gamma glutamyl transpeptidase (Bristol only)
15. Urinary concentration of alkaline phosphatase (Bristol only)

* an 'event' is described as a point when control of sedation is deemed to be acutely lost requiring immediate intervention. The intervention can involve more than one drug given over a short period of time to establish rapid control (within approximately a 30 minute window to allow safe titration if necessary).

Following study treatment phase

16. Time from stopping all sedation to being fully awake (determined by a sustained score of 4 on the alertness category of the COMFORT score).
17. Rebound hypertension
18. Signs of withdrawal measured using a 11 point assessment for abnormal behaviour (to be recorded until 5 days following treatment cessation or until discharge, whichever is soonest)
19. Withdrawal symptoms requiring clinical intervention (to be recorded until 5 days following treatment cessation or until discharge, whichever is soonest)

* Sustained for 2 hours or more.

Throughout the duration of study

20. Adverse events (to be recorded until 14 days post trial treatment cessation)

Health Economics

21. Cost per additional case of adequate sedation

9.4 Sample Size

Original and revised sample size calculations are included. Sample size revisions are necessary due to lower patient availability than expected.

a. Original trial sample size calculation

The proportion of children adequately sedated on midazolam is reported to be 0.65[60] with an expected proportion of 0.66 on clonidine. For a two-group large-sample normal approximation test of proportions with a two-sided 5% significance level to have 80% power to reject the null hypothesis that midazolam and clonidine are not equivalent (with margin of equivalence ± 0.10) would require 440 children in each group. The trial would therefore aim to recruit a total of 1000 children across both treatment groups to allow for approximately 10% loss to follow-up.

b. Revised sample size calculation for the primary outcome

The sample size calculations below use a 15% margin as agreed by the Principle Investigators and TSC members and indicate the statistical power that could be achieved with expected recruitment rate. Due to observed completeness of the data collected to date we have removed the 10% loss to follow up correction.

When the sample size in each group is 125, a two-group large-sample normal approximation test of proportions with a one-sided 0.025 significance level will have 64% power to reject the null hypothesis that the test and the standard are not equivalent (the difference in proportions, pT - pS, is 0.150 or farther from zero in the same direction) in favour of the alternative hypothesis that the proportions in the two groups are equivalent, assuming that the expected difference in proportions is 0.010 and the proportion in the standard group is 0.650.

9.5 Interim Monitoring and Analyses

SLEEPS will be monitored by an Independent Data and Safety Monitoring Committee (IDSMC) (see section 16.3). The IDSMC will be responsible for reviewing and assessing

recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. Missing data will be monitored and strategies developed to minimise its occurrence.

The IDSMC will initially meet prior to recruitment to agree the protocol and the IDSMC Charter. Subsequent timing of future meetings will be determined at the initial IDSMC meeting although it is anticipated that the meetings will occur at least annually. The IDSMC may request additional interim analyses if triggered by a concern regarding Sudden Unexpected Serious Adverse Reactions (SUSARs). All interim analysis results will be confidential to the IDSMC members and will not be for review by the Trial Management Group (except the statistical team preparing the IDSMC report).

The IDSMC will be asked to consider patient safety, particularly any Sudden Unexpected Serious Adverse Reactions (SUSARs) leading to death, alongside treatment efficacy when making their recommendation regarding continuation, amendment or discontinuation of the trial. Importantly, statistical considerations alone are not adequate for data monitoring due to the over-emphasis placed on the p-value resulting from hypothesis tests. Clinical judgment is essential to the process to account for unexpected adverse events and balance issues of safety and efficacy in light of any new external information. The decision to stop recruitment will depend on whether the results will be convincing to the medical community.

In order to estimate the effect of the clonidine and midazolam for the primary outcome the Haybittle-Peto approach will be employed for interim analyses with 99.9% confidence intervals calculated for the effect estimate. The final analysis will be undertaken after the final child has completed follow-up (1000) randomised in total) and 95% confidence intervals will be calculated. This method has been chosen to ensure that interim efficacy results would have to be extreme before early termination is recommended in order to be convincing to the clinical community. The method also minimises controversy regarding interpretation of the results from estimation and hypothesis testing at the final analysis. No inflation factor needs to be applied to the sample size using this approach.

9.6 Analysis Plan

The primary analysis will be by the intention to treat principle. The trial is defined as an equivalence trial for the primary outcome. For this outcome adhering to the ITT principle may not be conservative. Therefore a per protocol analysis will also be conducted to assess robustness of conclusions to protocol deviations. Equivalence for the primary outcome will be determined with margin of equivalence ± 0.15 as defined within the revised sample size calculation. For the secondary outcomes.statistical significance will be determined by a p-value of 0.05 or less. Dichotomous outcomes will be analysed using the chi square test, relative risks will be calculated and reported with 95% confidence intervals. Two sample t-tests will be used for normally distributed continuous outcomes with difference in means reported with 95% confidence intervals. Skewed continuous data will be log transformed. The log-rank test will be used for time to event outcomes and reported with Kaplan-meier curves and hazard ratios with 95% confidence intervals. Longitudinal data analysis using mixed models will be used to examine changes in comfort score and sedative and morphine doses over time between the groups. Regression models will be used as appropriate to investigate any chance imbalance of prognostic factors.

10 PHARMACOVIGILANCE

10.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

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

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

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in section 4.2.1.

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

- results in death
- is life-threatening* (participant at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Other important medical events

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

10.2 Reporting Procedures

10.2.1 Notes on Adverse Event Inclusions and Exclusions

10.2.1.1 Include

- Adverse reactions (10.2.1.1.1)
- Serious Adverse Events, SAR or SUSAR (10.2.1.1.2)

10.2.1.1.1 Adverse Reactions

Any untoward and unintended response that occurs in a participant in the trial that is suspected to be related to any dose administered of either Midazolam or Clonidine will be considered to be a suspected adverse reaction and must be reported.
All adverse reactions suspected to be related to either of the trial treatments should be reported on the Adverse Reaction Case Report Form, however for ease of completion a list of known adverse reactions will be provided on this CRF; the list will comprise of the following:

- Hypotension that requires intervention
- Bradycardia that requires intervention
- Hypertension following cessation of trial treatment

NB. All non-serious suspected adverse reactions will be recorded on the Adverse Reactions CRF. Non-serious adverse events do not need to be reported.

10.2.1.1.2 Serious Adverse Events, SAR, SUSAR

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that fulfil the criteria of a serious event (see section 10.1) must be reported using the Serious Adverse Event CRF, regardless of whether they are suspected to be related to the administration of Midazolam or Clonidine.

Serious Adverse Events do include the following:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment

Serious Adverse Events do not include:

- The disease/primary clinical condition being treated or associated symptoms/signs unless more severe than expected for the patient's condition
- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen

10.2.2 Reporting of Pregnancy

No pregnancy testing is planned as part of the study procedures. Patients who are known to be pregnant will be excluded from the study.

10.3 Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
The severity of ARs, SAEs, SARs and SUSARs must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine care
Moderate: interferes with routine care but does not require major intervention
Severe: impossible to perform routine care and requires major intervention

A distinction is drawn between serious and severe events. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, in the SLEEPS trial a severe adverse reaction need not necessarily be a Serious Adverse Reaction.

10.3.1 Procedures to be Followed in the Event of an Abnormal Laboratory Test or Abnormal Clinical Findings

Patients on PICU will be subject to laboratory tests necessary to the clinical management of the patient. However, documentation of laboratory data for the purpose of the trial will be limited to those laboratory parameters that are relevant to safety, study outcome measures and/or clinical outcome. These measurements are specifically listed in Table 5, Section 8. Responses to any abnormal laboratory values or clinical findings that are outwith the expectations of the primary disease or other concomitant treatments should be discussed by the local team (research nurse and clinician). If they cannot be fully explained by the primary clinical condition or the concomitant treatments and they fulfil any of the criteria in 10.1 for an AR, SAE, SAR or SUSAR then they should be appropriately reported.

10.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 6 below and should be recorded on the AR/SAE CRF.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 6: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. *N.B. An alternative cause for the AE should be given*
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "almost certainly" is an Adverse Drug Reaction.

All events judged by the investigator to be possibly, probably, or almost certainly related to the IMP, graded as serious and **unexpected** (refer to section 2.4.1 for expected side effects) should be reported as a SUSAR.

10.6 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.
When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: recovered; recovering; not recovered; fatal; unknown; recovered with sequelae (specifying with additional narrative)

10.7 Reporting Procedures

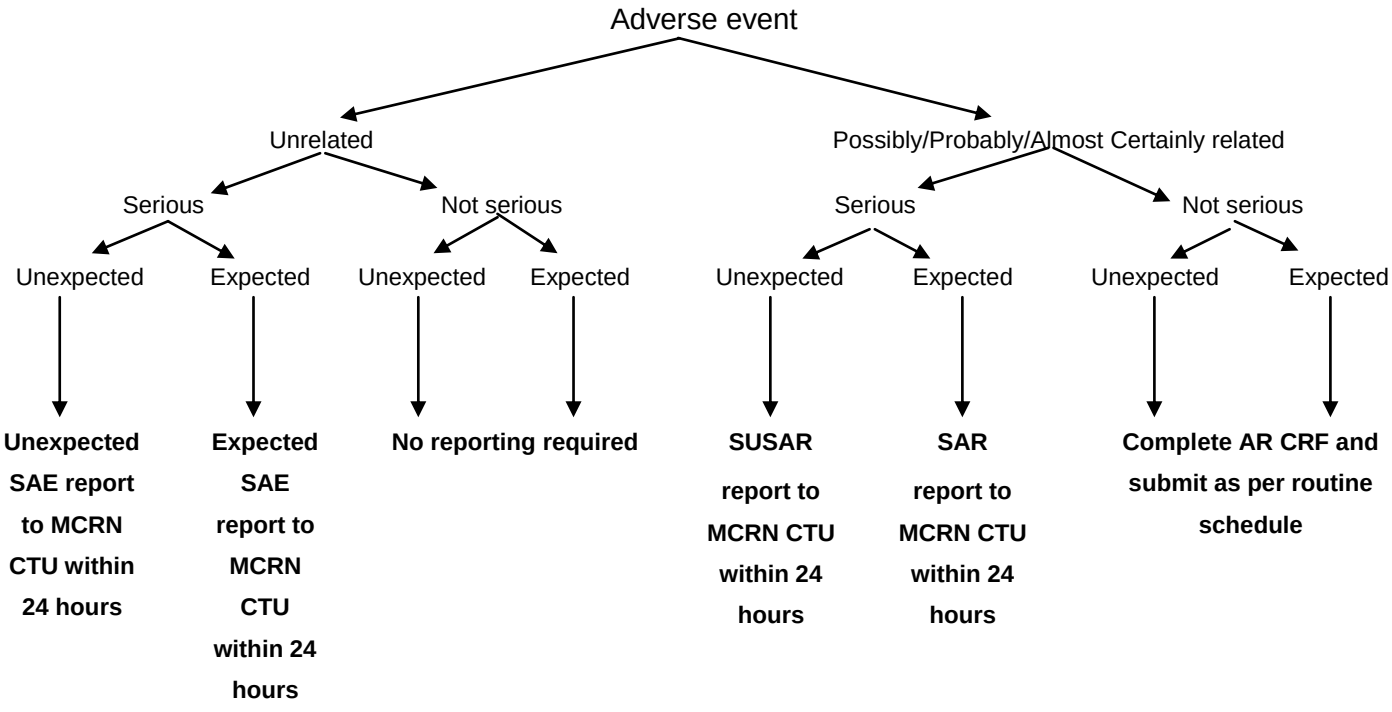
All adverse events fulfilling reporting criteria should be recorded on the CRF and submitted to the MCRN CTU within the defined timelines, beginning from the time that written informed consent is obtained (i.e. prior to undergoing any study-related procedure and/or receiving investigational medicinal product) and continuing for 14 calendar days after cessation of the investigational medicinal product. Depending upon the nature of the event, the reporting schedules below should be followed. Any questions concerning adverse event reporting should be directed to the MCRN CTU in the first instance. A flowchart is given on the following page to aid in determining reporting requirements.

10.7.1 Non serious ARs/AEs

Non-serious adverse events do not need to be reported.
Non-serious suspected adverse reactions, whether expected or not, should be recorded on an Adverse Reaction Case Report Form, which should be transmitted to the MCRN CTU within seven days of the form being completed.

10.7.2 Serious ARs/AEs/SUSARs

SARs, SAEs and SUSARs should be reported to the MCRN CTU within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.
The MCRN CTU will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & and Development Office.



10.8 Responsibilities - Investigator

The Investigator is responsible for reporting all ARs that are observed or reported during the study. The Investigator is also responsible for reporting all SAEs observed or reported during the study, regardless of their relationship to study product.
All SAEs must be reported immediately by the investigator to the MCRN CTU on an SAE form unless the SAE is specified in the protocol, as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

- Study identifier
- Study Center
- Randomisation number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

ii. The SAE form should be completed by the responsible investigator, the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that that it is a response to the investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team and faxed to the MCRN CTU immediately. The responsible investigator should check the SAE form, make changes as appropriate, sign and then re-fax to the MCRN CTU as soon as possible. The initial report shall be followed by detailed, written reports.
iii. Send the SAE form by fax (within 24 hours or next working day) to the MCRN CTU:

Fax Number: 0151 282 4721

iv. Staff at the institution should **notify** their local R&D department of the event (as per standard local procedure).
v. In the case of an SAE the participant must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
vi. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the MCRN CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
vii. The patient **must** be identified by randomisation number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

10.8.1 Maintenance of Blinding

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. In each report, seriousness, causality and expectedness should be evaluated for both of the trial treatments unless criteria have been fulfilled (section 7.6) and unblinding has taken place.
Cases that are considered serious, unexpected and possibly, probably or almost certainly related to one of the trial therapies (i.e. possible SUSARs) would have to be unblinded at the clinical trials unit prior to reporting to the regulator.

10.9 Responsibilities – MCRN CTU

The MCRN CTU is undertaking duties delegated by the trial sponsor, University Hospitals Bristol NHS Foundation Trust, Bristol, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place and, if required, the research ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the MCRN CTU is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the MCRN CTU first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the study participants, such as:
    a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the study population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;

c. A major safety finding from a newly completed animal study (such as carcinogenicity).
d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;

- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the study participants.

Staff at the MCRN CTU will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The MCRN CTU will also send an annual safety report containing a list of all SARs to regulatory authorities and MREC. Copies of the report will be sent to the Principal Investigator at all institutions participating in the trial

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).
The study protocol will be submitted for the consideration of the Riverside Multi-centre Research Ethics Committee once the final trial design has been approved and funded. All 12 participating centres will be subject to Site Specific Assessment by their Local Research Ethics Committee or their Research and Development Department prior to commencing recruitment. The specific ethical issues relate to:

- Limited time for consideration of trial entry; this trial is exploring sedative drugs in a critically ill population requiring prompt interventions. Due to its very nature, parents are required to be informed about the trial and make a decision regarding entry within hours of admission to PICU (unless it has been possible to approach the parents prior to surgery). Recruiting researchers will be experienced at imparting important information to parents in the PICU environment. Parents will be made aware of alternative treatments available and of their right to withdraw the child from the trial at any time without the child or family being subject to any resulting detriment.
- Informed consent in a paediatric population; The parent or legal representative of the child will have an interview with the investigator, or a designated member of the investigating team, during which opportunity will be given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. They will be provided with written information and contact details of the study personnel, who will also be readily available in the PICU, from whom further information about the trial may be obtained.
- An additional ethical issue is that due to the physical status of the target population it will not be possible for patient's to provide consent/assent, as applicable, at the time of trial entry. The ethics application will be supported by parent and child information sheets and parent and child consent/assent forms. Assent of trial participants, if appropriate, will be obtained as soon as their condition allows.

11.2 Ethical Approval

The trial protocol will be submitted for review by the Riverside Research Ethics Committee but must undergo site specific assessment by completion of a Site Specific Information form (SSI) and review by the relevant Local Research Ethics Committee (LREC) and local Research and Development (R & D) Department. If it is after April 2009 then site specific assessment will be carried out by the local R & D Department alone and not by the relevant LREC. A copy of local R & D approval and of the Patient Information and Consent form (PIC) on local headed paper should be forwarded to MCRN CTU before patients are entered.

11.3 Informed Consent Process

11.3.1 General

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Potential participants will be identified according to inclusion criteria by nurses or clinicians (informed about the study) either on transfer to PICU, prior to surgery or shortly after admission on PICU. The parent/legal representative will be approached either on transfer to PICU, prior to surgery or shortly after admission to PICU (if possible within 12 hours of admission). If the parent/legal representative is approached during transfer to PICU, the study will be mentioned and a summary information sheet will be provided. If the parent/legal representative is approached during transfer they will be given the full information sheet and approached for consent once the child has been admitted to PICU. A member of the research team will provide the parent/legal representative of the potential participants with written information about the trial, including contact details of the research team should they require further information or wish to contact a member of the research team.
Parental and age-and-stage-of-development appropriate Patient Information and Consent forms (PIC), approved by an independent ethical committee (IEC) will be issued by a member of the research team. The PIC will describe in detail the trial medicinal products to be compared, the trial procedures and potential risks/benefits. The patients' parent/legal representative will be asked to read and review the document. The PIC will emphasise that participation in the trial is voluntary and that the parent or guardian may, without the minor being subject to any resulting detriment, withdraw the minor from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated.
All parents/legally acceptable representatives and patients will be given opportunity to ask questions and will be given sufficient time to consider trial entry before consenting.
The consent form will request permission for the patient's General Practitioner to be informed of their involvement in the trial and also permission for personnel involved in the research or from regulatory authorities to have access to the individual's medical records.

11.3.2 Process of Informed Consent

The consent process will be carried out by a member of the research team identified in the trial signature and delegation log. The researcher will explain the objectives, trial interventions/products, potential risks/benefits of the research study to the parent/legal representative. They will explain the treatment options, including the conventional and generally accepted methods of treatment. If the parent/legal representative has been approached prior to surgery, eligibility needs to be confirmed upon arrival on PICU, therefore consent cannot be obtained until this time. Consent will be obtained from a parent* or the legally acceptable representative prior to any study related procedure being carried out. It will not be possible to obtain assent from patients prior to entry into the study as patients must be adequately sedated at screening. Therefore, assent will be obtained from patients where appropriate as soon as their condition allows.
Both the researcher taking consent and the parent or legally acceptable representative of the minor must personally sign and date the form. Once their condition allows, the patient should assent and sign and personally date a separate IEC-approved assent form which describes (in simplified terms) the details of the trial intervention/product, trial procedures and the potential risks involved. This form should also be signed and dated by the parent/legal representative. Assent forms do not substitute for the consent form signed by

the patient's legally acceptable representative. Where the child is unable to provide assent, this should be documented in the patient's medical notes.

The original copy of the signed consent/assent forms will be retained in the patient's medical notes. A copy will be returned to the MCRN CTU and a copy will be retained in the study file which must be made available for inspection when necessary. A further copy of the informed consent/assent document will be given to the patient's parent/legal representative.

*Legally this includes mothers and married fathers. Unmarried fathers of children born since 15 April 2002 in Northern Ireland, 1 December 2003 in England and Wales and 4 May 2006 in Scotland, if named on the child's birth certificate also have parental responsibility.
Unmarried fathers whose children were born before these dates, or afterwards if not named on the child's birth certificate, do not have automatically have parental responsibility. They can acquire parental responsibility by way of a Parental Responsibility Agreement with the child's mother or by obtaining a Parental Responsibility Order from the courts. Married step-parents and registered civil partners can acquire parental responsibility in the same ways.

11.4 Study Discontinuation

In the event that the study is discontinued, children will be reverted to normal standard care (Unit policy). Patients withdrawing early from trial treatment or ceasing trial medication after 7 days of treatment, in accordance with established clinical practice of "drug cycling", will also be reverted to normal standard care (Unit policy) but will not be unblinded unless protocol unblinding criteria are fulfilled (see Section 7.6).

12 REGULATORY APPROVAL

This trial will be registered with the MHRA and granted a Clinical Trial Authorisation (CTA). The CTA reference is 2008-000078-19

13 TRIAL MONITORING

13.1 Risk Assessment

In accordance with the MCRN CTU Standard Operating Procedure this trial has undergone a risk assessment, completed in partnership between the University of Liverpool, MCRN CTU, trial sponsor and chief investigator. In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.
The outcome of the risk assessment is expressed as a percentage, assigned according to the following categories:
Score ≤ 33% = Low risk
Score ≥34 to ≤ 67% = Moderate risk
Score ≥ 68 to ≤ 100% = High risk
The outcome of the SLEEPS trial risk assessment was a score of **21.67%** therefore it has been judged to be a **low risk** clinical trial

13.2 Source Documents

Source data*: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*
Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*
In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. The following CRF data should be consistent and verifiable with source data in source documents other than the CRF (eg medical record, laboratory reports and nurses' notes).

- Date of enrolment, date of subsequent study visits and date leaving study
- Relevant medical history and diagnosis
- Data for evaluation of (selected) eligibility criteria
- Dispension/administration of trial medication
- Concomitant medications (including changes) and diagnoses
- Sex
- Date of birth
- Adverse events (nature, dates)

Source documents should be identified prior to the clinical phase of the trial for each participating trial site.
For remaining data, where no prior record exists and which is recorded directly in the CRF, e.g. COMFORT score, withdrawal symptoms log, the Case Report Form will be considered the **source document**, unless otherwise indicated by the investigator. All such exemptions should be identified prior to the clinical phase of the trial.
In addition to the above, date(s) of conducting informed consent and assent process including date of provision of patient information, randomisation number, and the fact that the patient is participating in a clinical trial including treatment arms of midazolam and

clonidine should be added to the patient's medical record chronologically, ie, when these are allocated to the patient. Further, study treatment allocation should also be noted in the patient's medical record after unblinding of the study (see Section 7.6).

13.3 Data Capture Methods

13.3.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained using the following codes:

N/D (not done)	Use when a process or procedure was not done
N/A (not applicable)	Use when field does not apply
N/R (not recorded)	Use when the procedure was known to be done, but the data is unavailable or not written down
NK (not known)	Use when there is no other explained reason for the missing data

All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

13.4 Monitoring at CTU

Data stored at Clinical Trials Unit (CTU) will be checked for missing, unclear and unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, a data query will be raised and sent to the local site by post/fax/email. The site will respond to the queries and send a copy of the completed data query form to the CTU. The CTU will send reminders for any overdue and missing data.

13.5 Clinical Site Monitoring

13.5.1 Direct access to data

Once each site has recruited one or two patients, the trial coordinator plans to make a site visit to each to ensure that are no problems with complying with the protocol or completion of CRFs. Subsequent site monitoring visits may be deemed to be necessary as a result of central data checks. In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, eg patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

13.5.2 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.
Case report forms will be labelled with patient initials and unique trial registration and/or randomisation number.
Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the MCRN CTU by recruiting centres. This requires that name data will be transferred to the MCRN CTU, which is disclosed in the PIC. The MCRN CTU will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.5.3 Quality Assurance and Quality Control of Data

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This trial has undergone a risk assessment, the outcome of which indicates it to be a low risk trial. As such, site visits will be conducted and source data verification performed if indicated to be required as a result of central monitoring processes. To this end:

- The Principal Investigator, Research Nurse and designated Pharmacist from each centre will attend the trial launch meeting, coordinated by CTU in conjunction with the Chief investigator, Professor Andrew Wolf, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol
- The Trial Coordinator is to verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training
- The Trial Coordinator is to check safety reporting rates between centres
- The Trial Coordinator is to monitor screening, recruitment and drop-out rates between centres
- The Trial Coordinator is to conduct data entry consistency checks and follow-up data queries
- Independent oversight of the trial will be provided by the Data and Safety Monitoring Committee and independent members of the Trial Steering Committee

13.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, including the Investigator Trial File, for up to a maximum of 15 years or until the MCRN Clinical Trials Unit informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (eg in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The MCRN Clinical Trials Unit undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

14 INDEMNITY

SLEEPS is sponsored by University Hospitals Bristol NHS Foundation Trust and co-ordinated by the MCRN CTU in the University of Liverpool.

University Hospitals Bristol NHS Foundation Trust cover for negligent harm is in place through the Clinical Negligence Scheme for Trusts. If there is negligent harm during the study when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

For the purposes of the study Clinical Negligence is defined as:

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process". (NHS Indemnity: Arrangements for Clinical Negligence Claims in the NHS (October 1996))

15 FINANCIAL ARRANGEMENTS

This study is funded by the Health Technology Assessment programme (HTA) of the Department of Health. Contractual agreements will be in place between sponsor and collaborating sites that will incorporate financial arrangements.

15.1 Financial Support to Collaborating Sites

15.1.1 Research Nurse

Research nurses will be employed at each site for an equivalent of 0.2 FTE.

15.1.2 Pharmacy Department

The ampoules of study treatment will be received by the pharmacy department at each centre. Supplies will be released to each PICU for storage to ensure that there are always surplus supplies available on the Unit to enable a participant to be enrolled onto the study at any time. Provision of payment to support pharmacy costs (setup, storage, dispensing, reconciliation and GCP quality assurance), totalling £60 per patient randomised, has been allocated.

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

The Trial Management Group (TMG) will comprise Professor Andrew Wolf, Dr Carrol Gamble, Mr Andrew McKay, Ms Catherine Spowart, Mr Adam Sutherland, Dr Frank Potter and Dr Marie Horan. The TMG will be responsible for the day-to-day running and management of the trial and will meet monthly initially and then approximately 3 times a year.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson**,** Professor Adam Finn, Professor of Paediatrics, University of Bristol and 2 additional independent members; Dr Kerry Hood providing statistical expertise and Dr John Henderson, Reader in Paediatric Respiratory Medicine & Co-Director of Avon Longitudinal Study of Parents and Children (ALSPAC). Additional members will comprise Professor Andrew Wolf, Dr Carrol Gamble, Mr Andrew McKay, Ms Catherine Spowart, Mr Adam Sutherland, Dr Frank Potter and Dr Marie Horan. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. The TSC will receive reports from IDSMC and will convene shortly after each meeting of the IDSMC.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The independent Data and Safety Monitoring Committee (IDSMC) comprises 3 independent members; Dr Richard Howard (Consultant in Paediatric Anaesthesia and Pain Management, Great Ormond Street, Dr Mike Sury, Consultant Paediatric Anaesthetist, Great Ormond Street Hospital for Children and Professor Diana Elborne, Professor of Healthcare Evaluation, Queens Medical Centre, London, who has expertise in Medical Statistics

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to trial initiation. They will establish the IDSMC chairperson at this time and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 9.

The IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible after the close of the trial. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.
The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) and the CONSORT guidelines[61] will be respected. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.
BMJ guidance on authorship and contributorship (see http://bmj.com/advice/3.html) will be used to acknowledge the level and nature of contribution of key individuals in publications arising from the trial. The publication strategy shall lie under the jurisdiction of the Trial Steering Committee.

The protocol may be submitted for publication.

18 PROTOCOL AMENDMENTS

18.1 First substantial amendment Version 1.0 01/10/2008 to version 2.0 05/05/2009

Page No.	Comment
Throughout	Updated version and date
Page 2	Change to email address from sleeps@mcrnctu.org.uk to helpdesk@mcrnctu.org.uk
Page 3	Change to email address from sleeps@mcrnctu.org.uk to helpdesk@mcrnctu.org.uk. Addition of contact extension number of 0266 for Mary Perkins
Page 4	Change to email address from sleeps@mcrnctu.org.uk to helpdesk@mcrnctu.org.uk. Change of fax number from 00 44 (0) 151 252 5456 to 00 44 (0) 151 282 4721. Addition of contact extension number of 0266 for Mary Perkins Andrew McKay has replaced Ashley Jones as statistician.
Page 5	Change of Data Monitoring Committee member from Professor Peter Collins to Dr Mike Sury.
Page 18-19	Change in reporting requirements of adverse events. Text now states that only adverse reactions and Serious Adverse Events must be reported. Non-serious adverse events no longer need to be reported to alleviate the burden on PICU bedside nurses.
Page 19	Error in previous text. The sub-study is not limited to the Bristol centre.
Page 21	Addition of site specific assessment by local Research and Development Department. Inclusion criteria for centres changed from able to recruit a minimum of 82 patients in 2 years to 84 patients in 2 years.
Page 23	Text altered to remove requirement to report non-serious adverse events.
Page 25	Change in recording requirements of concomitant medications to alleviate the burden on PICU nurses. Only administration of inotropes, sedation and analgesia will be recorded at baseline. Other concomitant medications no longer need to be recorded at baseline.
Page 26	Storage temperature of trial treatment has changed from <25^{o}C to 30^{o}C or less. Following consultation with participating PICU's and measurement of maximum temperatures on PICU, there was a concern that temperatures were exceeding 25^{o}C on a regular basis. A review of the stability data for the trial treatments followed which has resulted in us being able to assign a 12 month shelf life at 30^{o}C or less. A change has now been made to the stability protocol to include "real time" at 6 months and 12 months time points for 30^{o}C/65% RH.
Page 26	Text has now been altered to state that the shelf life of the trial treatment is now 12 months (all subsequent batches will have a shelf life of 12 months).
Page 27	Clarification of the upper limit (50kg) for the largest weight group.
Page 27	Addition of text to state that a 21 gauge needle (0.81mm outer diameter) or smaller should be used to draw out the treatment from the vial to ensure that the extractable volume is adequate.
Page 28	Clarification that a dedicated line should be used for the administration of trial treatment and morphine has been provided. Advice regarding administration of trial treatment provided
Page 31	Storage temperature of trial treatment changed from <25^{o}C to 30^{o}C or less.

Page 31-32	Text altered to reflect change in concomitant medications recordings required to alleviate the burden on PICU bedside nurses. Throughout the trial, any medications administered at the time of a Serious Adverse Event, Serious Adverse Reaction or Suspected Unexpected Serious Adverse Reaction must be recorded. Aside from this: - All medications administered alongside the trial treatment do not need to be recorded. Only additional sedation and analgesia and use of muscle relaxant drugs administered alongside trial treatment now need to be recorded during trial treatment. - Text altered to state that following trial treatment concomitant medications should only be recorded for treatment of withdrawal symptoms.
Page 34	Addition of upper weight limit for Weight Group C for clarification
Page 35	Text altered to remove requirement to report non-serious adverse events.
Page 36	Text altered to remove requirement to report non-serious adverse events. Clarification that only adverse reactions and serious adverse events must be recorded.
Page 37	Clarification that fluid balance and clinical laboratory only to be recorded if these measurements are available. Addition of recording the number of ventilated days for each patient.
Page 38	Physical examination removed from schedule of study procedures. Addition of recording whether feeds are tolerated and whether bowels have opened.
Page 44	Addition of the upper limit (50kg) for the largest weight group.
Page 47-52	Text altered to remove requirement to report non-serious adverse events. Clarification that only adverse reactions and serious adverse events must be recorded. Clarification of reporting procedures and requirements. Diagram beneath 10.7.2 amended.
Page 55	Addition of site specific assessment by local Research and Development Department. If it is after April 2009 then site specific assessment will be carried out by the local R & D Department alone and not by the relevant LREC.
Page 64	Change of Trial Management Group member and Trial Steering Committee member from Ashley Jones to Andrew McKay.
Page 64	Change of Data Monitoring Committee member from Professor Peter Collins to Dr Mike Sury.
Page 84 & 85	Addition of upper weight limit for weight Group C for clarification

18.2 Non substantial amendment Version 2.0 05/05/2009 to version 2.1 14/09/2009

Throughout	Updated version and date
Throughout	Change of wording from subject to participant
Page 4	Addition of Jake Harley being authorised to sign the protocol and protocol amendments on behalf of the Sponsor Change of name from Fell to Spowart Change to telephone number of Andrew McKay from 252 5696 to 282 4725
Page 5	Diane amended to Diana
Page 10	Amendment to clarify that the study is an equivalence trial
Page 20	Change of spelling from Principle to Principal

Page 21	Clarification of length of time for recording withdrawal symptoms and adverse events
Page 25	Amendment to clarify that the study is an equivalence trial
Page 34	Amendment to clarify that the study is an equivalence trial
Page 36	Clarification of length of time adverse events are required to be reported
Page 43	Clarification of length of time for recording withdrawal symptoms
Page 44	Clarification of length of time for recording withdrawal symptoms and adverse events. Removal of word efficacy to clarify that this is an equivalence trial
Page 45	Amendment to analysis plan to clarify that the study is an equivalence trial
Page 50	Change of wording from subject to randomisation
Page 51	Change of wording from subjects to study participants Change of wording from subject to randomisation
Page 52	Change of wording from subjects to study participants
Page 57	Change of wording from subject to randomisation
Page 62	Change of name of Fell to Spowart Diane amended to Diana
Page 63	Addition of text to say that the protocol may be submitted for publication
Page 73	Addition of Dr Margrid Schindler as Qualified Physician responsible for Trial-Site Related Medical Decisions at Above Site

18.3 Substantial Amendment Version 2.1 14/09/2009 to Version 3.0 05/10/1009

Throughout	Updated version and date
Page 22	Addition of “Blood biochemistry and urinalysis” to secondary endpoints Addition of “Percentage of time spent adequately sedated” to secondary endpoints
Page 31	Change of text from PICU to pharmacy
Page 43	Addition of blood biochemistry and urinalysis to secondary endpoints. Addition of “Percentage of time spent adequately sedated” to secondary endpoints
Page 57	Removal of text marking source data sections of CRF with Ⓢ.
Page 73	Removal of Participating Sites from protocol (Change of PI from Dr Kate Parkins at Royal Liverpool Children’s Hospital to Dr Frank Potter. Change of Trust name from Royal Liverpool Children’s Hospital to Alder Hey Children’s NHS Foundation trust). Participating sites are now a supporting document.
Throughout	Amendments to order of appendices and references to appendices following removal of participating sites from appendices.

18.4 Substantial Amendment 3.0 05/10/2010 to Version 4.0 06/05/2010

Throughout	Updated version and date
Page 3	Amendment to contact details for Funder
Page 4	Amendment to Chief Investigator’s telephone and fax number
Page 5	Details for data manager added
Page 10	Amendment from “likely to require intubation and ventilation for more than 48 hours” to “likely to require intubation and ventilation for more than 24 hours” Clarification that the trial will be conducted in 12 of the sites listed on the Participating Sites document

Page 11	Text added to box at bottom of page to explain actions to be taken regarding morphine should a child be oversedated on minimum trial sedation and minimum morphine Text amended to show that all patients are followed up until 14 days following trial treatment cessation rather than until hospital discharge
Page 19	Amendment to state that if an intervention is required to treat a withdrawal symptom this will be recorded on the withdrawal symptom chart rather than the concomitant medications page
Page 24	Text to explain that children who are born before 37 weeks gestation are eligible for the trial if they are a minimum of 30 days post delivery and their corrected gestation is 37 weeks or more 48 hours amended to 24 hours for Inclusion Criterion b Amendment from 3 months to 1 month to Exclusion Criteria l
Page 25	Clarification that a need to commence haemodialysis or haemofiltration will result in the child being withdrawn from the trial Amendment from withdrawal CRF to End of Study CRF
Page 26	Amendment of “Screening and Enrolment Log” to “Screening Log” Addition of text to state that if a child is likely to be suitable for the trial following surgery, the parent or legally acceptable representative of the child can be approached prior to surgery. The physical examination has been removed from the baseline assessments (physical examinations were removed in a previous amendment but this had been missed) “Time sedation therapy administered at trial entry stopped” removed. Text to state that baseline assessments can be completed retrospectively
Page 27	Addition of lower storage temperature for trial medications of 2^{o}C
Page 28	Addition of text to state which colour pack each weight group will be presented in
Page 32	Addition of lower storage temperature for trial medications of 2^{o}C
Page 33	Clarification of recording of concomitant medications required to treat withdrawal symptoms
Page 35	Addition of text to state that if a child is receiving the minimum infusion s of trial sedation and morphine and the child is oversedated, the morphine can be further reduced by an increment of 10micrograms/kg/hr to 10 micrograms/kg/hr, providing there are no requirements for analgesia. If the child is still oversedated, the morphine can be stopped (as long as there are no analgesic requirements) although the trial sedation should continue.
Page 35	Amendment from three months to one month for co-enrolment guidelines
Page 36	Amendment from 48 hours to 24 hours Clarification that for the first 24 hours following treatment cessation, withdrawal symptoms will be recorded 4 hourly, whether on the ward or in PICU
Page 38	Amendment to text to state that fluid balance will only be recorded during trial treatment
Page 39	Addition of Day 7 to Treatment Days Amendment to text to state that fluid balance will only be recorded during trial treatment
Page 43	Removal of text saying that the child’s GP and/or District nurse will be asked to contact the family and provide follow up information to the recruiting centre.
Page 50	Amendment from “below” to “on the following page”
Page 54 & 55	Addition of text to state that the parent/legal representative can be approached prior to their child having surgery Clarification that the consent process can be carried out by a member of the research team identified in the trial signature and delegation log

	Removal of text 'at this stage'
Page 55	Removal of text saying that if a child is unable to assent this will be documented on the age and stage of development specific PISC
Page 59	Amendment to presentation of missing data codes and addition of N/R and N/K codes. Amendment to Monitoring at CTU section detailing the assessment of data and how data queries will be processed
Page 63	Removal of Dr Simon Nadel from the Trial Management Group and Trial Steering Committee. Addition of Dr Frank Potter and Dr Marie Horan to the Trial Management Group and Trial Steering Committee
Page 77	Muscle Tone and Alertness swapped order in COMFORT score Amendment from "Blood Pressure/Heart Rate below baseline" to "Blood Pressure/Heart Rate 15% below baseline"
Page 81	Amendment from "Blood Pressure/Heart Rate below baseline" to "Blood Pressure/Heart Rate 15% below baseline"
Page 82	Removal of "2 minute" from Muscle Tone.
Page 84	Addition of text to state which colour pack each weight group will be presented in
Page 86	Addition of text to state that if a child is receiving the minimum infusion s of trial sedation and morphine and the child is oversedated, the morphine can be further reduced by an increment of 10micrograms/kg/hr to 10 micrograms/kg/hr, providing there are no requirements for analgesia. If the child is still oversedated, the morphine can be stopped (as long as there are no analgesic requirements) although the trial sedation should continue.

18.5 Substantial Amendment 4.0 06/05/2010 to version 5.0 01/03/2011

Throughout	Updated version and date
Page 9	Addition of 'ICU = Intensive Care Unit' to Glossary
Page 10	1000 removed Reduction from 24 hours to 12 hours for number of hours child is likely to require intubation and ventilation for. Increase from 48 hours to 120 hours for the period children can be entered into the trial following admission to PICU. Addition of 'ICU' as child may have been admitted to ICU initially rather than PICU. 12 changed to 10 for number of participating sites
Page 11	Updated flowchart replaced previous flowchart to explain change to protocol regarding administration of trial treatment and morphine.
Page 16	'The Specials Clinical Manufacturing Unit' changed to 'SCM Pharma'
Page 23	Definition of treatment failure for Secondary Endpoint number 12 changed from the administration of three rescue boluses within any one 12 hour period to three 'events' where rescue medication(s) are needed to re-establish sedation or pain control occurring within any one 12 hour period during trial treatment. Description of an 'event' provided.
Page 24	Change to inclusion/exclusion criteria: - Reduction from 24 hours to 12 hours for number of hours child is likely to require intubation and ventilation for (inclusion criterion b) - Increase from 48 hours to 120 hours for the period children can be entered into the trial following admission to PICU. Addition of 'ICU' as child may have been admitted to ICU initially rather than PICU. (inclusion criterion c)

- Clarification regarding exclusion of patients with severe neuromuscular problems/impairment (exclusion criterion h)
- Addition of exclusion criteria 'Previously participated in SLEEPS trial' (exclusion criterion m)

Page 25 Addition of 'A requirement for continuous infusion of muscle relaxants' as a reason for patients to be withdrawn from the trial intervention.

Page 26 Addition of text to state that parents of eligible patients can be approached regarding the trial during transfer and a summary information sheet can be given to the parents at this point.
Removal of recording 'inotropic administration' as a baseline assessment.
Addition of recording of previous sedation and analgesic therapy

Page 28 'The Specials Clinical Manufacturing Unit' changed to 'SCM Pharma'

Page 33 Addition of chlorpromazine, haloperidol and promethazine to allowed supplementary anaesthesia.

Page 34 Addition of guidance doses for allowed concomitant medications.

Page 35 Adjustment to trial treatment and morphine administration to allow bedside nurse to evaluate child for pain and conscious level to decide whether trial treatment or morphine should be adjusted.
Treatment failure changed from requiring three rescue doses within a 12 hour period to three 'events' where rescue medication are needed to re-establish sedation or pain control occur within a 12 hour period. Description of an 'event' given.
Removal of guidance dose for fentanyl.

Page 36 Adjustment to trial treatment and morphine administration to allow bedside nurse to evaluate child for pain and conscious level to decide whether trial treatment or morphine should be adjusted.
Addition of text to say that when a COMFORT score of below 17 is recorded, the score must remain below 17 for 2 consecutive hours before the morphine is reduced.

Page 37 Addition of text to say that when a COMFORT score of below 17 is recorded, the score must remain below 17 for 2 consecutive hours before the morphine is reduced. Clarification of adjustments to trial sedation and morphine provided.
Text added to say that the trial sedation can be temporarily stopped if the morphine has been stopped and the COMFORT score still remains below 17.

Page 38 24 hours changed to 12 hours.
Addition of text 'and morphine' as the COMFORT score will dictate whether increases or decreases in study medication AND morphine occur.

Page 39 Addition of text to say that following trial treatment cessation, the only COMFORT score category that needs to be completed is 'Alertness' and that if sedation is still required following trial treatment cessation then the COMFORT score should continue to be measured hourly until the child is stable on the new sedative.

Page 41 Increase from 48 hours to 120 hours for the period children can be entered into the trial following admission to PICU. Addition of 'ICU' as child may have been admitted to ICU initially rather than PICU.

Page 46 Change to description of treatment failure to three 'events' where rescue medication are needed to re-establish sedation or pain control occurring within any one 12 hour period during trial treatment.
Description of event provided

Page 48 Revised sample size calculation provided.
Margin of equivalence altered to 0.15

Page 58	Addition of text to state that parents of eligible patients can be approached regarding the trial during transfer and a summary information sheet can be given to the parents at this point.
Page 83	Addition of text to say that baseline for blood pressure and heart rate should be recalculated on a daily basis (or occasionally more frequently). Text 'or since the previous COMFORT score' added.
Page 86	Addition of text to say that baseline for blood pressure and heart rate should be recalculated on a daily basis (or occasionally more frequently).
Page 88	Guidance provided regarding interpretation of heart rate and blood pressure in the use of the COMFORT score.
Page 92 - 93	Adjustment to protocol regarding administration of trial treatment and morphine: - Bedside nurse to evaluate child for pain and conscious level to decide whether trial treatment or morphine should be adjusted. - When a COMFORT score of below 17 is recorded, the score must remain below 17 for 2 consecutive hours before the morphine is reduced. - Trial sedation can be temporarily stopped if the morphine has been stopped and the COMFORT score still remains below 17.

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APPENDICES

Appendix A: COMFORT Score

		Score
MUSCLE TONE		
Muscles Totally Relaxed; No Muscle Tone		1
Reduced Muscle Tone		2
Normal Muscle Tone		3
Increased Muscle Tone and Flexion of Fingers and Toes		4
Extreme Muscle Rigidity and Flexion of Fingers and Toes		5
CALMNESS/AGITATION		
Calm		1
Slightly Anxious		2
Anxious		3
Very Anxious		4
Panicky		5
RESPIRATORY RESPONSE		
No coughing and No Spontaneous Breathing		1
Spontaneous Breathing with No Resistance to the Ventilator		2
Occasional Cough or Resistance to the Ventilator		3
Actively Breathes against the Ventilator		4
Fights Ventilator/Coughing or Choking		5
PHYSICAL MOVEMENT		
No Movement		1
Occasional Slight Movement		2
Frequent Slight Movement		3
Vigorous Movement Limited to Extremities		4
Vigorous Movements Include Torso and Head		5
BLOOD PRESSURE MAP BASELINE		
Blood Pressure 15% Below Baseline		1
Blood Pressure Consistently at Baseline		2
Infrequent Elevations of 15% or more (1-3)		3
Frequent Elevations of 15% or more (more than 3)		4
Sustained Elevation of >15%		5
HEART RATE BASELINE		
Heart Rate 15% below Baseline		1
Heart Rate Consistently at Baseline		2
Infrequent Elevations of 15% or more (1-3)		3
Frequent Elevations of 15% or more (more than 3)		4
Sustained Elevation of >15%		5
ALERTNESS		
Deeply asleep		1
Lightly asleep		2
Drowsy		3
Fully awake and alert		4
Hyper-Alert		5
FACIAL MUSCLES		
Facial Muscles totally Relaxed		1
Facial muscle tone normal; No tension		2
Tension Evident in Some Facial Muscles		3
Tension Evident Throughout Facial Muscles		4
Facial Muscles Contorted/Grimacing		5
		TOTAL

COMFORT Pain Scale

The COMFORT scale is a behavioural, unobtrusive method of measuring distress in unconscious and ventilated infants, children and adolescents. This scale has eight (8) indicators:

- alertness
- calmness/agitation
- respiratory response
- physical movement
- blood pressure
- heart rate
- muscle tone
- facial tension

Each indicator is scored between 1 and 5 based upon the behaviours exhibited by the patient. Patients should be observed unobtrusively during the previous hour. The total score is derived by adding the scores of each indicator. See the COMFORT scale behavioural descriptors and scoring. Total scores can range between 8-40. A score of 17-26 generally indicates adequate sedation and pain control. Due to the complexity of measuring blood pressure and heart rate, this scale is used primarily for patients in a critical care setting.

C1. COMFORT Scale Procedures

1. The rater reviews the bedside medical flow chart and calculates baseline, upper and lower limits for the heart rate and mean arterial pressure. The baseline for both blood pressure and heart rate will initially be an average of the measurements taken in the 4 hours prior to trial entry. This should be recalculated on a daily basis (or occasionally more frequently) for each patient if this is felt to be clinically appropriate. Values 15% above and below are calculated before beginning observation to allow rapid assessment of variability.
2. The rater will make their observations during the previous hour or since the previous COMFORT score. The rater will make an appraisal of the movement, body position, facial expression, response to environmental stimuli, etc., according to the COMFORT score.
3. Over the observational period of 1 hour for each assessment, the rater observes the trend of heart rate and mean arterial pressure
and determines whether these are within 15% of the baseline.
4. Approximately 10 seconds before the end of the observation period, the observer rates muscle tone based upon patient response to rapid and slow flexion of a noninstrumental extremity (i.e. elbow or knee without an IV, tape, arterial line or physical restraint). A wrist or ankle may be used if no other joint is available.
5. The rater moves away from the patient and records ratings for each scale. The most extreme (distressed) behaviour observed during the observation period is scored on each variable. The total COMFORT score is derived as the total of the scores of the eight dimensions.

C2. COMFORT Scale Scoring

1. Alertness

Rates the patient's response to ambient stimulation in the environment including responses to sound (noises from monitors, intercoms, people talking, pagers, etc.), movement, light, etc. To rate this category, no stimulus is introduced by the observer.

1. Deeply asleep: The state of least responsiveness to the environment. The patient's eyes are closed, breathing is deep and regular, and the patient shows minimal responses to changes in the environment.
2. Lightly asleep*:* The patient has their eyes closed throughout most of the observation period, but still responds somewhat to the environment as evidenced by slight movements, facial movements, unsuccessful attempts at eye openings, etc.
3. Drowsy*:* The patient closes their eyes frequently or makes labored attempts to open eyes and is less responsive to the environment.
4. Alert and awake*:* The patient is responsive and interactive with the environment, but without an exaggerated response to the environment. The patient's eyes
remain open most of the time or open readily in response to ambient stimuli.
5. Hyper-alert*:* The patient is hyper-vigilant, may be wide-eyed, attends rapidly to subtle changes in the environmental stimuli and has exaggerated responses to environmental stimuli.

Guidelines: If two or more of the following items achieve a score of two or higher, then the child is classified as lightly asleep – Respiratory response, Physical Movement, Muscle Tone.

2. Calmness/Agitation

Rates the patient's level of emotional arousal and anxiety.

1. Calm*:* The patient appears serene and tranquil. There is no evidence of apprehension or emotional distress.
2. Slightly anxious: The patient is not completely calm. The patient shows slight apprehension and emotional distress.
3. Anxious*:* The patient appears somewhat apprehensive and emotionally distressed, but remains in control.
4. Very anxious: The patient appears very apprehensive. Emotional distress is apparent but the patient remains somewhat in control.
5. Panicky: The patient's total demeanor conveys immediate and severe emotional distress with loss of behavioural control.

3. Respiratory Response

Rates the patient's oral and respiratory responses to an endotracheal tube and intermittent ventilation.

1. No coughing or no spontaneous respiration: Only ventilator generated breaths are apparent. No respiratory movement is apparent between ventilator breaths. No oral movement or chest wall movement occurs except as created by the ventilator.
2. Spontaneous respiration: The patient breathes at a regular, normal respiratory rate in synchrony with the ventilator. No oral movement or chest wall movement occurs which is contrary to the ventilator movement.
3. Occasional cough/resists ventilator: The patient has occasional oral or chest wall movement contrary to the ventilator pattern. The patient may occasionally breathe out of synchrony with the ventilator.
4. Actively breathes against ventilator: The patient has frequent oral or chest wall movement contrary to the ventilator pattern, coughs regularly, or frequently breathes out of synchrony with the ventilator.
5. Fights ventilator - coughs/chokes/gags: The patient actively makes oral or chest wall movement contrary to the ventilator pattern, coughs and/or gags in a manner which may interfere with ventilation.

4. Physical Movement

Rates frequency and intensity of physical movement.

1. None: The patient shows complete absence of independent movement.
2. Occasional, slight movements: The patient shows three or fewer small amplitude movements of the fingers or feet, or very small head movement.
3. Frequent, slight movement: The patient shows more than three small amplitude movements of the fingers or feet, or very small head movements.
4. Vigorous movements of extremities only: The patient shows movements of greater amplitude, speed or vigor of hands, arms or legs. The head may move slightly. Movement is vigorous enough to potentially disrupt cannulas.
5. Vigorous movements of extremities, torso and head: The patient shows movements of greater amplitude, speed or vigor of the head and torso, such as head thrashing, back arching or neck arching. Extremities may also move. Movement is vigorous enough to potentially disrupt placement of an endotracheal tube.

Guidelines: Occasional movement is defined as < once/minute
Frequent movement is defined as > once/minute

5. Blood Pressure

Mean arterial blood pressure (MAP) rates the frequency of elevations above (or below) a normal baseline. The baseline may need to be reset on a daily basis or occasionally more frequently depending on changes in clinical conditions (eg. change in temperature or the addition of inotropes etc). Each re-evaluation will set the cardiovascular baselines for each “rating period”.
At the beginning of the rating period, baseline, 15% below baseline and above baseline values are recorded on the rating sheet in an easily observable location. The rater observes the monitor for mean arterial blood pressure during the observational period of an hour and records, with a hash mark, each observation above or below the baseline. Ratings are made upon the number of readings above the baseline.

1. Blood pressure 15% below baseline.
2. Blood pressure consistently at baseline.
3. Infrequent elevations of 15% or more (1-3 during observation period).
4. Frequent elevations of 15% or more (more than 3 during observation period).
5. Sustained elevation greater than or equal to 15%.

Guidelines: The baseline to use initially for blood pressure will be an average of the measurements taken hourly over the 4 hours previous to trial entry. Following this, the baseline should be recalculated on a daily basis for each patient (or occasionally more frequently), if this is felt to be clinically appropriate for the individual.

6. Heart Rate

Heart rate score is based on the frequency of elevations above (or below) a normal baseline. The baseline may need to be reset on a daily basis or occasionally more frequently depending on changes in clinical conditions (eg. change in temperature or the addition of inotropes etc). Each reevaluation will set the cardiovascular baselines for each “rating period”. At the beginning of the rating period, baseline, 15% above baseline and below baseline values are recorded on the rating sheet in an easily observable location. The observer observes the heart rate throughout the hour and records, with a hash mark, each episode of elevation above the baseline or episodes below the baseline.
Ratings are made based upon the number of readings above the baseline.

1. Heart rate 15% below baseline.
2. Heart rate consistently at baseline.
3. Infrequent elevations of 15% or more (1-3 during observation period)
4. Frequent elevations of 15% or more (more than 3 during observation period)
5. Sustained elevation greater than or equal to 15%

Guidelines: The baseline to use initially for blood pressure will be an average of the measurements taken hourly over the 4 hours previous to trial entry. Following this, the baseline should be recalculated on a daily basis for each patient (or occasionally more frequently), if this is felt to be clinically appropriate for the individual.

Guidance on interpretation of heart rate and blood pressure values

If heart rate and blood pressure values are inappropriate to the rest of the COMFORT score due to other clinical events, then the heart rate and blood pressure should be scored as **2: ie at baseline.** For example, if a patient has a temperature of 39^{o}C and a heart rate of 190 bpm which is not consistent with a child that otherwise has COMFORT score criteria that indicate adequate analgesia and sedation, then the heart rate will be scored as 2.

7. Muscle Tone

Muscle tone is assessed in relation to normal tone in a patient who is awake and alert.
The rating is based upon patient response to rapid and slow flexion and extension on a non-instrumented extremity (i.e. elbow or knee without an IV, tape, arterial line or physical restraint). A wrist or ankle may be used if no other joint is available. This rating is the only one that requires active intervention by the rater and is performed at the end of the observation period.

1. Relaxed/None: Muscle tone is absent. There is no resistance to movement.
2. Reduced muscle tone: The patient shows less resistance to movement than normal, but muscle tone is not totally absent.
3. Normal muscle tone: Resistance to movement is normal.
4. Increased tone/flexion-fingers/toes: The patient shows resistance to movement that is clearly greater than normal, but the joint is not rigid.
5. Extreme rigidity/flexion-fingers/toes: Muscle rigidity is the patient's predominant state throughout the observation period. This may be observed even without manipulating an extremity.

8. Facial Tension

Facial tension assesses tone and tension of facial muscles. The standard of comparison is a patient who is awake and alert.

1. Relaxed: The patient shows no facial muscle tone, with absence of normal mouth and eye closing. The mouth may look slack and the patient may drool. Brow smooth.
2. Normal tone: The patient shows no facial muscle tension with mouth and eyes closing appropriately. Small movements of the lips, mouth or tongue. Brow smooth.
3. Some tension: This does not include sustained tension of muscle groups such as the brow, forehead or mouth but you may see a frown or eye squeezing.
4. Full facial tension: The patient shows notable, sustained tension of facial muscle groups including the brow, forehead, mouth, chin or cheeks.
5. Hyper-alert: The patient demonstrates facial grimacing with an expression that conveys an impression of crying, discomfort and distress. This generally includes extreme furrowing of brow and forehead and contortion of the mouth.

Appendix B: Withdrawal Symptoms

The following symptoms were identified by a prospective survey of 338 paediatric intensive care patients across 20 UK PICUs[62].
Please indicate with an 'X' in the appropriate box any occurrence of these symptoms observed after cessation of trial sedation therapy and grade them according to the three point severity scale.
If you consider that you are observing a withdrawal symptom not described by these terms, please write this in one of the free boxes, together with the severity & duration observed:

Record every four hours on PICU and daily on ward.

Date (dd/mon/yyyy)																
Time (24 hour clock)																
SYMPTOM	None	Mild	Mod	Severe	None	Mild	Mod	Severe	None	Mild	Mod	Severe	None	Mild	Mod	Severe
Tremors/Convulsions																
Irritability																
Hallucinations																
Inconsolably distressed																
Anxiety																
Restless/Hyperactive																
Other abnormal behaviour																
Nausea/Vomiting																
Nightmares																
Sweating																
Pain																
Other (specify): _____																
Other (specify): _____																

* **Mild**: does not interfere with routine activities; **Moderate**: interferes with routine activities; **Severe**: impossible to perform routine activities

Appendix C: Scheme for Drug Delivery

Blinded Syringe Production and Presentation

The ampoules of study treatment will be stored in the PICU drugs cupboard at room temperature.

The nurse will prepare the study drug for infusion according to which weight group the patient falls into:

(a)<10kg (yellow pack)
(b) 10-25kg (blue pack)
(c) >25kg-50Kg (pink pack)

Morphine will be prepared as per usual fashion (on the PICU by the nursing staff)

Preparations and strength
a) <10Kg
MIDAZOLAM: put 50mg (5ml) Midazolam to total of 50 ml 5% dextrose (1mg/ml).
CLONIDINE: put 750micrograms (5ml) clonidine to total of 50ml 5% dextrose(15micrograms/ml).

b)10-25Kg
MIDAZOLAM put 62.5mg (6.25ml) midazolam to total of 50ml 5% dextrose (1.25mg/ml)
CLONIDINE: put 937.5micrograms (6.25ml) clonidine to total of 50ml 5% dextrose (18.75micrograms/ml)

c)>25Kg-50Kg
MIDAZOLAM put 250mg (25ml) to total of 50ml 5% dextrose (5mg/ml).
CLONIDINE put 3750micrograms (25ml) to total of 50ml in 5%dextrose (75micrograms/ml)

MORPHINE (a,b,c) put 1mg/kg in 50 ml 5% dextrose

Dose Range
Strength a
MIDAZOLAM Dose range is 0.05ml/kg/hr (50micrograms/kg/hr) to 0.2ml/kg/hr (200micrograms/kg/hr).
CLONIDINE Dose range is 0.05ml/kg/hr (0.75micrograms/kg/hr) to 0.2ml/kg/hr (3micrograms/kg/hr).

Strength b)
MIDAZOLAM Dose range is 0.04ml/kg/hr (50micrograms/kg/hr) to 0.16ml/kg/hr (200micrograms/kg/hr)
CLONIDINE Dose range is 0.04ml/kg/hr (0.75micrograms/kg/hr) to 0.16ml/kg/hr (3micrograms/kg/hr).

Strength c)
MIDAZOLAM Dose range 0.01ml/kg/hr (50micrograms/kg/hr) to 0.04ml/kg/hr (200micrograms/kg/hr).

CLONIDINE Dose range 0.01 ml/kg/hr (0.75micrograms/kg/hr) to 0.04ml/kg/hr (3micrograms/kg/hr).

Morphine (a,b,c) 0.5ml/hr (10micrograms/kg/hr) and 3ml/hr (60micrograms/kg/hr)

Loading
a)<10Kg
MIDAZOLAM Load for 1 hour at start of trial with 0.2mlkg over 1hour (200micrograms/kg/hr).
CLONIDINE Load for 1 hour at start of trial with 0.2ml/kg over 1 hour (3micrograms/kg/hr).
MORPHINE Load with 100micrograms/kg over 15minutes

b)10-25Kg
MIDAZOLAM Load for 1 hour at start of trial with 0.16ml/kg over 1hour (200micrograms/kg/hr)
CLONIDINE Load for 1 hour at start of trial with 0.16ml/kg over 1hour (3micrograms/kg/hr)
MORPHINE Load with 100micrograms/kg over 15minutes

c) >25Kg-50Kg
MIDAZOLAM Load for 1 hour at start of trial with 0.04ml/kg over 1 hour (200micrograms/kg/hr).
CLONIDINE Load for 1 hour at start of trial with 0.04ml/kg over 1 hour (3micrograms/kg/hr).
MORPHINE Load with 100micrograms/kg over 15minutes

Maintainance and Incremental Change

a),10Kg
MIDAZOLAM Start infusion at 0.1ml/kg/hr (100micrograms/kg/hr). Change in steps of 0.05ml/kg/hr..
CLONIDINE Start infusion at 0.1ml/kg/hr (1.5micrograms/kg/hr). Change in steps of 0.05ml/kg/hr.
MORPHINE Start at 20micrograms/kg/hr (1ml/hr)

b) 10-25Kg
MIDAZOLAM Start infusion at 0.08ml/kg/hr (100micrograms/kg/hr). Change in steps of 0.04ml/kg/hr
CLONIDINE Start infusion at 0.08ml/hr/kg/hr (1.5micrograms/kg/hr). Change in steps of 0.04ml/hr/kg
MORPHINE Start at 20micrograms/kg/hr (1ml/hr)

c) >25Kg-50Kg
MIDAZOLAM Start infusion at 0.02ml//kg/hr (100micrograms/kg/hr). Change in steps of 0.01ml//kg/hr
CLONIDINE Start infusion at 0.02ml/kg/hr (1.5micrograms/kg/hr). Change in steps of 0.01ml/kg/hr.
MORPHINE Start at 20micrograms/kg/hr (1ml/hr)

Scheme for adjustment of Infusions

1. Load and start infusions
2. COMFORT score hourly (target $\leq 26 \geq 17$)
3. Increase or decrease study medication infusion based on hourly COMFORT score as per schematic diagram (pg 10) and using the incremental changes described above. Protocol dictates that the decision to increase or decrease study medication or morphine should be made hourly according to the COMFORT score. If the patient has a COMFORT score of above 26 then nurses at the bedside will need to assess the patient for pain and their conscious level to determine whether morphine or trial sedation should be increased. If the patient is judged to be in pain then the morphine should be increased by 10micrograms/kg/hr (up to a maximum of 60micrograms/kg/hr). If the patient is judged to have a lack of sedation then the trial drug should be increased by the designated amount (see Table 1, section 7.3). Only one incremental change of either trial medication or morphine can occur per documented COMFORT score.
4. If the patient develops a COMFORT score of 27 or greater in between hourly assessments, it is acceptable to formally score the patient and increase the sedative infusion delivery before the formal hourly assessment. This will need to be recorded.
5. The maximum dose of Clonidine is 3micrograms/kg/hr and the maximum dose of midazolam is 200micrograms/kg/hr.
6. If sedation is re-established and COMFORT score falls to below 17 and a score of less than 17 is sustained for 2 hours (two subsequent COMFORT scores), reduce morphine or trial sedation infusion incrementally as clinically indicated (according to subsequent COMFORT scores) down to a minimum of 20micrograms/kg/hr for morphine or down to the minimum trial infusion rate for the appropriate weight group.
7. However, if sedation remains inadequate after an hour of maximum study drug and maximum morphine (60micrograms/kg/hr), treatment failure will have been deemed to have occurred. Switch to alternate sedation as per unit policy. Continue with measurements of COMFORT and blood pressure described above.
8. If the minimum trial infusion rate and a morphine infusion rate of 20micrograms/kg/hr is administered and the COMFORT score of the child is still below 17, then if there are no analgesic requirements, the morphine can be further decreased by an increment of 10micrograms/kg/hr to 10micrograms/kg/hr. If at the subsequent COMFORT score, the COMFORT score is still below 17, the morphine can be stopped (providing there are no analgesic requirements). If at the subsequent COMFORT score, the COMFORT score is still below 17, the trial sedation can be temporarily stopped.
9. If during study a painful procedure is required necessitating additional anaesthesia or analgesia this can be provided. Trial medication should remain at the same infusion rate throughout this period until the effects of other drugs have worn off. Drugs used may include: Propofol, volatile anaesthetic agents, thiopentone, ketamine, fentanyl morphine, midazolam, or diazepam. Careful documentation of these concomitant medications will be made and evaluations as per the study will continue. Muscle relaxants are also permissible for procedures where this is deemed necessary by the independent clinician.
10. If during the infusion there is a sudden and extreme loss of sedation control (which may be associated with incidental manipulations,

nursing cares or simply with sudden arousal), it is permissible to deliver a rescue dose of additional intravenous analgesia or sedation as deemed necessary. This will be recorded. The trial will then proceed as before with upward adjustment of trial medications as per protocol. However if three such episodes requiring intervention occur within a 12 hour period, then this will terminate the study for that patient which will then be described as a treatment failure.