Safety profiLe, Efficacy and Equivalence in Paediatric intensive care Sedation

ST001TEM01 - Statistical Analysis Plan

Eudract No. 2008-000078-19

	ORIGINATED BY
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Change Control

Updated SAP version no.	Section number changed	Description of change	Date changed	Name
2.0	All outcomes with a chi-square test	• If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value.	04/07/2013	Andrew McKay (Trial Statistician)
2.0	7.2 – Randomisation checking	• Delete sentence: "A frequency table of unassigned treatment allocations for the missed randomisation numbers will be presented split by strata and centre" as this was used during the trial for monitoring purposes.	04/07/2013	Andrew McKay (Trial Statistician)
2.0	7.3 – Recruitment	• Summary of screening logs.	04/07/2013	Andrew McKay (Trial Statistician)
2.0	7.4 – Baseline comparability of randomised groups	• Stated that all baseline characteristics will be summarised by mean/median with standard deviation/IQR but in addition minimum and maximum values will be presented. • 'Time from sedation to consent: for each individual sedative' will be reported as 'time from any sedative to consent'. Numbers taking each specific seditive will be presented split by treatment group. • 'Analgesia taken prior to consent: number of patients taking each analgesia' will be reported as 'any analgesia prior to consent'. Numbers taking each specific analgesias will be presented split by treatment group. • Those drugs that have both analgesic and sedation properties will be counted as both an analgesic and sedative. • Any analgesias/sedatives not listed in this SAP will be summarised	04/07/2013	Andrew McKay (Trial Statistician)

Updated SAP version no.	Section number changed	Description of change	Date changed	Name
		and sent to the Chief Investigator for categorisation.		
2.0	7.5 – Completeness of follow-up	• Add text "A table will be presented for reasons patients came off treatment." • Clarification that further clarification for the patients lost to follow-up is for those lost to follow-up during the treatment phase.	04/07/2013	Andrew McKay (Trial Statistician)
2.0	16 – Analysis of primary efficacy outcome	• Change "The total number of hours sedated will also be broken down by reason for end of sedation (Sedation no longer required, AE, completed 7 days treatment, treatment failure, other) and summarised as above." to "Reason for end of sedation will be summarised for all patients included in the primary analysis".	04/07/2013	Andrew McKay (Trial Statistician)
2.0	17.2/17.3 – Time to reach the maximum permitted dose of sedation / morphine	• Will present the median with 95% confidence interval from the Kaplan-Meier plot for each treatment group along with 25% and 75% quartiles with 95% confidence intervals.	04/07/2013	Andrew McKay (Trial Statistician)
2.0	17.4/17.5 – Profile in rise of cumulative sedative / morphine infusion	• Make clear that it is the new treatment start time (*NTST*) that will be used as the start time. • Data in the format of rates per hour and not doses per hour as previously stated. • For multiple recordings of rates within the same hour will take the mean. • Patients with no dose data post-*NTST* will be excluded from the analysis. • Add 1-standard error bars to the mean profile plot. • Make clear the least square means are for cumulative sedative/morphine. • Just for morphine outcome 17.5, add: "These data are recorded on the CRF as an infusion rate mls/hr and do not need standardising	04/07/2013	Andrew McKay (Trial Statistician)

Updated SAP version no.	Section number changed	Description of change	Date changed	Name
		for each patient based on their weight at trial entry like for sedative."		
2.0	17.8 – Fall in blood pressure judged by clinician to require intervention	• A Cochran-Armitage trend test will be performed and *p*-value presented for total number of days a patient had a fall in blood pressure judged by clinician to require intervention.	04/07/2013	Andrew McKay (Trial Statistician)
2.0	17.10 – Supplementary analgesia required during sedation	• Multiple recordings of the same analgesic within an hour will be counted as one 'instance'. For the specific analgesias and analgesias split by reason summary multiple recordings of the same analgesic within an hour will be counted as multiple events. • A Cochran-Armitage trend test will be performed and p-value presented for number of instances of analgesia. • Start time for outcome will be the treatment start time (*TST*) to include any analgesias recorded during the loading dose.	04/07/2013	Andrew McKay (Trial Statistician)
2.0	17.11 – Daily urine output	• Results are presented both in terms of 'average daily output' and 'average hourly output'. However, the differences in means/medians will only be performed with corresponding *p*-value presented on the 'average daily output' to reflect the title of the outcome.	04/07/2013	Andrew McKay (Trial Statistician)
2.0	17.16 – Time from stopping all sedation to being fully awake	• Main analysis will now censor those patients that have a final alertness score of 4 or 5 collected but do not have a score of 4 or 5 for the previous hour. A risk ratio, 95% confidence interval and *p*-value will be presented. • These patients will be included in sensitivity analyses assuming that (1) they are fully awake and this is the reason why no more final alertness scores were taken and (2) they are not fully awake. Risk ratios, 95% confidence intervals and *p*-values will be presented. • Will present the median with 95% confidence interval from the Kaplan-Meier plot for each treatment group along with 25% and	04/07/2013	Andrew McKay (Trial Statistician)

Updated SAP version no.	Section number changed	Description of change	Date changed	Name
		75% quartiles with 95% confidence intervals. • Will present the *p*-value from the log-rank test for each treatment group. • Change "*awake_time_length* (mins)" to say "*awake_time_length* (hours)".		
2.0	17.18 – Signs of withdrawal measured using a 11 point assessment for abnormal behaviour	• Main analysis will now exclude assessments with any missing observations for any of the 11 withdrawal symptoms. Best and worst case sensitivity analyses will be performed.	04/07/2013	Andrew McKay (Trial Statistician)
2.0	18.2 – Analyses of missing data – Primary outcome	• In the sentence "* Patients that had no primary outcome data collected or did not complete the loading dose period will be assumed to have not been adequately sedated for at least 80% of the total evaluated time spent sedated (*AS*=1)" there was a typo. Last part changed to "(*AS*=0)".	04/07/2013	Andrew McKay (Trial Statistician)
2.0	Appendix A: CONSORT diagram	• Updated the CONSORT flow diagram.	04/07/2013	Andrew McKay (Trial Statistician)
2.0	Appendix C: Health Economics Analysis Plan	• Health economics analysis plan updated by health economics team.	04/07/2013	Stavros Petrou & Angela Boland (Health Economics)

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1 Table of Contents

2 Introduction

This Statistical Analysis Plan (SAP) provides a detailed and comprehensive description of the pre-planned final analyses for the study “SLEEPS: Safety profiLe, Efficacy and Equivalence in Paediatric intensive care Sedation”.

This study is 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, Clinical Trials Research Centre (CTRC) Clinical Trials Unit (CTU) Standard Operating Procedures (SOPs) and EU Directive 2001/20/EC, and the UK statuory instrument No. 1916: The Human Medicines Regulations 2012.

This statistical analysis plan details the intended analyses and should be clear and detailed enough to be followed by any statistician. This will prevent the introduction of bias or data dredging.

These planned analyses will be performed by the trial statistician under the supervision of the lead statistician. The analysis results will be described in a statistical analysis report, to be used as the basis of the primary research publications according to the study publication plan.

All analyses are performed with standard statistical software (SAS version 9.1 or later). The finalised analysis datasets, programs and outputs will be archived following Good Clinical Practice guidelines and SOP TM021 Archiving procedure in CTRC. The testing and validation of the statistical analysis programs will be performed following SOP ST001.

3 Definitions

ALT	Alanine transaminase
AR	Adverse reaction
AST	Aspartate transaminase
BP	Blood pressure
bpm	beats per minute
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CS	COMFORT Score
CTRC	Clinical Trials Research Centre
ECMO	Extracorporeal membrane oxygenation
FiO_2	Fraction of inspired oxygen
GCS	Glasgow Coma Score

ICU	Intensive Care Unit
IDSMC	Independent Data and Safety Monitoring Committee
INR	International Normalized Ratio
IQR	Inter-quartile range
ITT	Intention-to-treat
IU/l	international units per litre
IV	Intravenous
kg	kilogram
kPa	kilopascal
MAP	Mean arterial pressure
mmHg	millimetre of mercury
mmol/l	millimoles per litre
µmol/l	micromoles per litre
NTST	New treatment start time
$PaCO_2$	Partial pressure of carbon dioxide in the blood
PaO_2	Partial pressure of oxygen in the blood
PDF	Portable document format
PELOD score	Paediatric Logistic Organ Dysfunction score
PI	Principal Investigator
PICSSG	Paediatric Intensive Care Society Study Group on Sedation
PICU	Paediatric Intensive Care Unit
PK/PD	Pharmacokinetic/Pharmacodynamic
PP	Per-protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SLEEPS	Safety profiLe, Efficacy and Equivalence in Paediatric intensive care Sedation
SUSAR	Suspected Unexpected Serious Adverse Reactions
TK/TD	Toxicokinetic/Toxicodynamic
TMG	Trial Management Group
TOST	Two One-Sided Tests
TSC	Trial Steering Committee
TST	Treatment start time
TTCT	Trial treatment cessation time
WBC	White blood cells
Wt	Weight

4 Study design and objectives

This study is a prospective, multi-centre, randomised, double-blind, equivalence study comparing clonidine and midazolam as intravenous sedative agents in critically ill children. The study is conducted in 10 centres throughout the United Kingdom.

The primary objective of this study is to determine whether intravenous clonidine can provide equivalent control of sedation in the critically ill child when compared to intravenous midazolam.

The secondary objective of this study is 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. There are 21 secondary endpoints listed in section 5.2.

Patients were stratified by centre and weight and randomised equally (1:1) between the two groups:

1) Clonidine
2) Midazolam

Weight was not considered to be a prognostic indicator but randomisation was stratified by this factor to reduce wastage and costs associated with preparing all treatment packs to contain sufficient medicinal product to allow for higher weight participants.

Separate randomisation lists were generated for each stratum in STATA using simple block randomisation with random variable block length:

- Weight Group A (<10kg) – block sizes of 4 and 6
- Weight Group B (10kg-25kg) – block sizes of 4 and 6
- Weight Group C (>25kg-50kg) – block sizes of 2 and 4.

Randomisation
A member of the research team completed the randomisation Case Report Form to ensure that the patient met the eligibility criteria for randomisation.

Treatment packs
Pharmacy issued a number of blinded treatment packs for storage on PICU so that patients could be recruited into the trial at any time. The trial treatment packs were pre-randomised and sequentially numbered therefore upon randomisation the next pack in the sequence for the appropriate weight group was selected. The 3 different weight groups for the trial had a different coloured box (Weight Group A = <10kg (yellow), Weight Group B = 10kg-25kg (blue), Weight Group C = >25kg-50kg (pink)). The randomisation log was completed and the start date, patient's initials and the

patient's weight were completed on the treatment pack (by the member of the research team randomising the patient).

4.1 Sample size calculations

Sample size calculations were undertaken using NQuery Advisor software version 4.0.

Original and revised sample size calculations are included. Sample size revisions were 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[3] 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 Principal Investigators (PIs) and Trial Steering Committee (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.

4.2 Interim analysis

SLEEPS was monitored by an Independent Data and Safety Monitoring Committee (IDSMC). The IDSMC was responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The extent and type of missing data were monitored and strategies developed to minimise its occurrence.

The IDSMC initially met prior to recruitment to agree the protocol and the IDSMC Charter. Subsequent timing of future meetings was determined at the initial IDSMC

meeting although it was anticipated that the meetings would occur at least annually. The IDSMC could request additional interim analyses if triggered by a concern regarding Sudden Unexpected Serious Adverse Reactions (SUSARs). All interim analysis results were confidential to the IDSMC members and not available for review by the Trial Management Group (except the statistical team preparing the IDSMC report).

The IDSMC considered patient safety, particularly any Sudden Unexpected Serious Adverse Reactions (SUSARs) leading to death, alongside treatment efficacy when making recommendations 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 should depend upon whether the results are convincing to the medical community.

In order to estimate the effect of clonidine and midazolam for the primary outcome it was planned that the Haybittle-Peto approach would be employed for requested interim analyses with 99.9% confidence intervals calculated for the effect estimate. This method was chosen to ensure that interim efficacy results would have to be extreme before recommending early termination in order to be convincing to the clinical community.

5 Study Outcomes

5.1 Primary Outcome

Adequate sedation defined as at least 80% of total evaluated time spent sedated within a COMFORT score range of 17 to 26.

5.2 Secondary Outcomes

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 medications are needed to re-establish sedation or pain control occurring 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 (see also separate SAP for health economics)

6 Inclusion / Exclusion Criteria

6.1 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

6.2 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.

7 Description of study population

7.1 Representativeness of study sample and patient throughput

A CONSORT[1] flow diagram (appendix A) will be used to summarise the number of patients who were:

- assessed for eligibility at screening
  - eligible at screening
  - ineligible at screening*
- eligible and randomised
- eligible but not randomised*

- received the randomised allocation
- did not receive the randomised allocation*
- lost to follow-up*
- discontinued the intervention*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided.

7.2 Randomisation checking

A check will be performed to identify occurrences of missing randomisation numbers and whether any had been randomised out of sequence. Any missing randomisation numbers and numbers randomised out of sequence will be presented in a summary table showing randomisation pack number(s) and reason for not being used split by centre.

7.3 Recruitment

Screening logs will be summarised by site with numbers of patients not eligible, eligible and not randomised and randomised presented with reasons given (including reasons for non-consent) where available. Other free-text reasons will be summarised appropriately.

A recruitment summary table will be presented showing the following for each centre: centre code, hospital name, dates site opened/closed to recruitment, dates of first/last randomisation and total number randomised.

A recruitment graph will also be presented displaying the cumulative recruitment, cumulative target recruitment and number of sites open to recruitment for each month from the trial opening to closing recruitment.

7.4 Baseline comparability of randomised groups

Patients in each treatment group (clonidine and midazolam) will be described with respect to the following:

- *General*: gender*, age at consent#, weight of child#, weight group*, reasons for admission to PICU*, COMFORT Score total at trial entry#, Glasgow Coma Score total#, pacing system*

- *Cardiovascular*: systolic blood pressure[#], diastolic blood pressure[#], heart rate[#], average BP MAP over 4 hours previous to trial entry[#], average heart rate over 4 hours previous to trial entry[#]
- *Pulmonary*: PaO_2[#], FiO_2[#], $PaCO_2$[#]
- *Neurologic*: pupillary reaction*
- *Inotropic support*: number of children receiving inotropic support at trial entry[#]
- *Clinical Laboratory Results*: prothrombin time[#], INR[#], WBC[#], platelets[#]. Other laboratory results collected at baseline will be presented alongside the post-baseline measurements[#]
- The paediatric logistic organ dysfunction (PELOD) score[#]
- *Time from any sedative to consent*[#] e.g. alimemazine, chloral hydrate, clonidine[$], ketamine[$], lorazepam, midazolam, morphine, trimeprazine,
- *Any analgesia taken prior to consent*: number of patients taking each analgesia* e.g.clonidine[$], fentanyl, ketamine[$], paracetamol
- *Start of treatment*: time from consent to commencing trial treatment[#].

* Categorical
# Continuous
$ These drugs have both analgesic and sedation properties.

Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by mean, SD and range if data are normal and median, IQR and range if data are skewed. Minimum and maximum values will also be presented for continuous data. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted.

For ‘time from any sedative to consent’, if patients have multiple recordings of any sedatives then the date of the first recording will be used to calculate the time to consent. Numbers and percentages of patients that were on each specific seditive will be presented.

In addition to ‘any analgesia taken prior to consent’, the numbers and percentages of patients that took at least one of each analgesia will be presented.

Those drugs that have both analgesic and sedation properties will be counted as both an analgesic and sedative. Any analgesias/sedatives not listed above will be summarised and sent to the Chief Investigator for categorisation.

The paediatric logistic organ dysfunction (PELOD) score[4] is a measure of severity of illness calculated using routine PICU measurements. It is calculated using the scoring system below:

Table 5-1: PELOD SCORING SYSTEM[4]

	Scoring system			
	0	1	10	20
Organ dysfunction and variable				
Neurological*				
Glasgow coma score	12–15	7–11	4–6	3
	and		**or**	
Pupillary reactions	Both reactive	NA	Both fixed	NA
Cardiovascular†				
Heart rate (beats/min)				
<12 years	≤195	NA	>195	NA
≥12 years	≤150	NA	>150	NA
	and		**or**	
Systolic blood pressure (mm Hg)				
<1 month	>65	NA	35–65	<35
1 month–1 year‡	>75	NA	35–75	<35
1–12 years‡	>85	NA	45–85	<45
≥12 years	>95	NA	55–95	<55
Renal				
Creatinine (μmol/L)				
<7 days	<140	NA	≥140	NA
7 days–1 year‡	<55	NA	≥55	NA
1–12 years‡	<100	NA	≥100	NA
≥12 years	<140	NA	≥140	NA
Respiratory§				
PaO_2 (kPa)/FIO_2 ratio	>9·3	NA	≤9·3	NA
	and		**or**	
$PaCO_2$ (kPa)	≤11·7	NA	>11·7	NA
	and			
Mechanical ventilation§	No ventilation	Ventilation	NA	NA
Haematological				
White blood cell count ($\times 10^9$/L)	≥4·5	1·5–4·4	<1·5	NA
	and	**or**		
Platelets ($\times 10^9$/L)	≥35	<35	NA	NA
Hepatic				
Aspartate transaminase (IU/L)	<950	≥950	NA	NA
	and	**or**		
Prothrombin time¶ (or INR)	>60 (<1·40)	≤60 (≥1·40)	NA	NA

PaO_2=arterial oxygen pressure. FIO_2=fraction of inspired oxygen. $PaCO_2$=arterial carbon dioxide pressure. INR=international normalised ratio. *Glasgow coma score: use lowest value. If patient is sedated, record estimated Glasgow coma score before sedation. Assess patient only with known or suspected acute central nervous system disease. Pupillary reactions: non-reactive pupils must be >3 mm. Do not assess after iatrogenic pupillary dilatation. †Heart rate and systolic blood pressure: do not assess during crying or iatrogenic agitation. ‡Strictly less than. §PaO_2: use arterial measurement only. ¶Percentage of activity. PaO_2/FIO_2 ratio, which cannot be assessed in patients with intracardiac shunts, is considered as normal in children with cyanotic heart disease. $PaCO_2$ may be measured from arterial, capillary, or venous samples. Mechanical ventilation: the use of mask ventilation is not counted as mechanical ventilation.

The data for all the separate elements of the PELOD score were collected at baseline. Within the Neurological section of the PELOD score, the verbal section of the Glasgow Coma Scale (GCS) was problematic as the majority of children in the SLEEPS trial were too young to be able to talk, so this is inappropriate, even if measured before ventilation (which for PELOD to be accurate, it should be). For the older children, this same section was inappropriate because the nurses were most likely be completing the GCS after the children had been ventilated so the children would have a tube down their throat thus not be able to talk. In both of these cases the verbal section of the GCS was recorded as 'unobtainable' on the CRFs/database and ignored in the calculation of the GCS total.

The PELOD scores will be calculated for each patient with complete data for all of the elements of PELOD shown in Table 5-1. Those patients where the verbal section of the Glasgow Coma Scale (GCS) is unobtainable their GCS total will be calculated across completed elements only. The PELOD scores will be summarised (across treatment groups and split by treatment group) by mean, SD and range if data are normal and median, IQR and range if data are skewed overall and then split by those with completed verbal score and those without a verbal score.

To investigate the impact of the missing verbal section of the GCS on the balance of the PELOD scores for the two treatment groups the following will be performed:

1. The numbers and % of patients without a fully completed neurological score (due to the verbal section of the GCS not being applicable) will be summarised by treatment group to check the balance between treatment groups.

2. Two sensitivity analyses will be performed calculating summary measures of the PELOD scores (mean, SD and range if data are normal; median, IQR and range if data are skewed) for each treatment group:

    - Sensitivity analysis 1: with the patients without a completed verbal section of the GCS removed.
    - Sensitivity analysis 2: with the value of 1 imputed (lowest value on the GCS i.e. worst case) for the patients without a completed verbal section of the GCS.

Again tests of statistical significance will not be undertaken; rather the clinical importance of any imbalance will be noted.

7.5 Completeness of follow-up

Completeness of follow-up will be presented in the form of a CONSORT flow diagram. See section 7.1 for details. A table will be presented for reasons patients came off treatment.

Further clarification for the patients lost to follow-up during the treatment phase will be presented as line listings with the following details given:

- Time on trial treatment (hours)
- Any AEs
- Any SAEs/SUSARs.

8 Follow up assessments

The schedule of study procedures is given in the Table 8-1 below.

TABLE 8-1: 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 sub study 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).

9 Study Outcomes

All patients who died should be included in the primary outcome analysis using all data up to the point of death. Inclusion in secondary outcomes is dependent upon the outcome being observed prior to death. This strategy is considered reasonable given the expected number of deaths. A sensitivity analysis will be specified if monitoring indicates a level greater than 10%.

9.1 Primary outcome

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

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. 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 protocol uses the COMFORT score to determine whether increases or decreases in study medication and morphine are required. (See Appendix A of the SLEEPS trial protocol for COMFORT score and guide for using the assessment).

The COMFORT scores were assessed once an hour during administration of trial treatment but if clinician judgement indicated that it was necessary to increase or decrease study medication before the hour had ended, a COMFORT score was recorded and adjustments made to ensure the comfort and safety of patients. COMFORT scores were collected on the 'during trial treatment PICU patient bedside days 1-8' CRF from the start of trial treatment until treatment cessation. COMFORT scores recorded for a particular hour relate to those obtained during the previous hour i.e. a COMFORT score recorded for hour 03:00 was recorded taking into account the patient observations over the previous hour 02:01-03:00. Patients were on trial treatment for a maximum of 7 days. Details of how to calculate the primary outcome from the COMFORT score measurements are given in section 15 'Analysis of primary efficacy outcome'.

9.2 Secondary outcomes

During study treatment phase

1. Percentage of time spent adequately sedated – this uses the COMFORT score data that was recorded at least hourly and collected on the 'during trial treatment PICU patient bedside days 1-8' CRF. Details of how to calculate this outcome from the COMFORT score data is given in section 17.1.

2. Time to reach the maximum permitted dose of sedation – this uses the dose of sedative that was recorded at least hourly and collected on the 'during trial treatment PICU patient bedside days 1-8' CRF and recorded in mls/hr. The dose of sedative is calculated using the patients' weights (actual/formula) recorded on the 'Randomisation' CRF. If the formula has been used rather then the actual weight it is asked to be recorded at a later time, if possible on the 'Actual weight' CRF. On this CRF it says to continue using the weight on the randomisation CRF for dosing (i.e. formula weight). Therefore, even if the actual weights are recorded later on the formula weights were still used. Details of how to calculate this outcome are given in section 17.2.

3. Time to reach the maximum permitted dose of morphine – this uses the dose of morphine that was recorded at least hourly and collected on the 'during trial treatment PICU patient bedside days 1-8' CRF and recorded in mls/hr. Details of how to calculate this outcome are given in section 17.3.

4. Profile in rise of daily cumulative sedative infusion – this uses the dose of sedative that was recorded at least hourly and collected on the 'during trial treatment PICU patient bedside days 1-8' CRF and recorded in mls/hr. Details of how to calculate this outcome are given in section 17.4.

5. Profile in rise of daily cumulative morphine infusion – this uses the dose of morphine that was recorded at least hourly and collected on the 'during trial treatment PICU patient bedside days 1-8' CRF and recorded in mls/hr. Details of how to calculate this outcome are given in section 17.5.

6. Maximum permitted dose of sedative reached – this uses the dose of sedative that was taken at least hourly and collected on the 'during trial treatment PICU patient bedside days 1-8' CRF and recorded in mls/hr. Details of how to calculate this outcome are given in section 17.6.

7. Maximum permitted dose of morphine reached – this uses the dose of morphine that was taken hourly and collected on the 'during trial treatment PICU patient bedside days 1-8' CRF and recorded in mls/hr. Details of how to calculate this outcome are given in section 17.7.

8. Fall in blood pressure judged by clinician to require intervention – these data are collected on the 'retrospective during trial treatment days 1-8' CRF from the question "Has an incidence of hypotension occurred that required intervention that was not expected for the patient's condition?". A "Yes/No" answer was given.

9. Increased inotropic support required in 1st 12 hours after randomisation – these data are collected on the 'retrospective during trial treatment day 1' CRF from the

question “Has the patient required increased inotrophic support in the first 12 hours following randomisation?”. A “Yes/No” answer was given. This question was added to the CRF partway through the trial so patients that will have been randomised prior to this will not have had this data collected. At the end of the trial data management will contact sites to see if this data can be obtained from patient notes/charts.

10. Supplementary analgesia required during sedation – the supplementary analgesia (sedation analgesia and muscle relaxants given for "loss of sedation control") taken for a particular hour and the reason why it was needed is collected on the ‘during trial treatment PICU patient bedside days 1-8’ CRF. This was collected as coded data using the codes: A = Agitated/Discomfort, B = Limit Movement, C = Painful/Clinical Procedure, D = Pyrexia, E = Other (describe below), F = General Care, these codes will be used for analysis.

11. Daily urine output – total fluids in, urine out and total fluids out data are collected approximately hourly on the ‘retrospective during trial treatment days 1-8’ CRF. Dates and times the data are taken is also recorded. Details of how to calculate this outcome are given in section 17.11.

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 occurring within any one 12 hour period during trial treatment – these data are collected on the ‘during trial treatment PICU patient bedside days 1-8’ CRF. The date and time that the study treatment was stopped was recorded where the reason for treatment discontinuation was recorded as “Treatment failure”.

    * 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).

13. Blood biochemistry and urinalysis – the data for the blood biochemistry parameters (sodium, potassium, chloride, urea, creatinine, bilirubin, ALT, AST and alkaline phosphatase) and urinalysis (urea and creatinine) parameters were collected on the ‘randomisation’ CRF and then once daily on the ‘retrospective during trial treatment days 1-8’ CRF. The measurements collected on the ‘retrospective during trial treatment days 1-8’ CRF, whether the results are normal/abnormal and whether abnormal results were clinically significant or expected for the patients’ condition were all collected. The data for the urinalysis (urea and creatinine) parameters were collected once daily on the ‘retrospective during trial treatment days 1-8’ CRF. The measurements, whether the results are

normal/abnormal and whether abnormal results were clinically significant or expected for the patients' condition were all collected.

14. Urinary concentration of gamma glutamyl transpeptidase (Bristol only) – the PK/PD sub-study at the Bristol site did not go ahead as planned so these data were not collected and therefore is unable to be analysed.

15. Urinary concentration of alkaline phosphatase (Bristol only) – the PK/PD sub-study at the Bristol site did not go ahead as planned so these data were not collected and therefore is unable to be analysed.

Following study treatment phase

16. Time from stopping all sedation to being fully awake (determined by a sustained** score of 4 or 5 on the alertness category of the COMFORT score) – the time the patients stop sedation is recorded on the 'during trial treatment PICU patient bedside days 1-8' CRF. The time being fully awake as described above is captured on the '24 hours following trial treatment cessation patient bedside follow-up day 1' CRF. Details of how to calculate this outcome are given in section 17.16.

    ** Sustained for 2 hours or more.

17. Rebound hypertension – these data were collected on the adverse reactions (ARs) and serious adverse events (SAEs) CRFs. On the '24 hours following trial treatment cessation patient bedside follow-up day 1', 'PICU post-treatment follow-up days 2-5' and 'ward post-treatment follow-up days 1-5' CRFs there is a question "Has the child experienced any reactions (e.g. hypotension, hypertension, bradycardia) that you think were related to the trial treatment (clonidine or midazolam)?". Any instances where "Yes" is selected will be cross-checked against the AR and SAE CRFs. If no instance of hypotension, hypertension or bradycardia is present on the AR and SAE CRFs this will be queried.

18. Signs of withdrawal were measured using an 11 point assessment for abnormal behaviour (to be recorded until 5 days following treatment cessation or until discharge, whichever is soonest) – these data were collected on the '24 hours following trial treatment cessation patient bedside follow-up day 1', 'PICU post-treatment follow-up days 2-5' and 'ward post-treatment follow-up days 1-5' CRFs. Details of how to calculate this outcome are given in section 17.18.

19. Withdrawal symptoms requiring clinical intervention (to be recorded until 5 days following treatment cessation or until discharge, whichever is soonest) – these data were collected on the '24 hours following trial treatment cessation patient bedside follow-up day 1', 'PICU post-treatment follow-up days 2-5' and 'ward

post-treatment follow-up days 1-5' CRFs from the question "Has any medication been required to treat withdrawal symptoms?". A "Yes/No" answer is given. Assessment of withdrawal symptoms began when sedation ceased. They were 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 was soonest. Details of how to calculate this outcome are given in section 17.19.

Throughout the duration of study

20. Adverse events (to be recorded until 14 days post trial treatment cessation) – these data were collected on the adverse reactions (ARs) and serious adverse events (SAEs) CRFs.

Health Economics

21. Cost per additional case of adequate sedation – The health economic analyses are being undertaken by a separate health economics team lead by Stavros Petrou. A separate health economic analysis plan has been developed and agreed and is listed in Appendix C.

Toxicokinetic & Toxicodynamic Sub-study

22. The TK/TD sub-study at the Bristol site did not go ahead as planned so these data were not collected and therefore is unable to be analysed.

10 Description of compliance with treatment

Allocated trial treatments were administered via IV by PICU personnel. All administrations were recorded on drug prescription sheets and infusion charts documenting rate of infusion. Any deviations from this such as incorrect actions taken to the patients' comfort scores, etc, were recorded as protocol deviations (see section 14).

Details were collected on:

- any patients that were not given the intended drug (clonidine or midazolam) and crossed over onto the other treatment arm.
- withdrawals from study (due to withdrawal of consent or another reason).

Reasons will be presented where available.

11 Trial monitoring

SLEEPS will be monitored by an Independent Data and Safety Monitoring Committee (IDSMC). Please see section 4.2 for details.

The SLEEPS data management plan includes details of ongoing monitoring performed by data management. Also, the trial coordinator undertook site visits after the first two patients were randomised at each site to address issues raised by data management.

12 Unblinding of randomised treatments

Treatment packs were identically packaged, therefore the risk of unblinding additional participants unintentionally was minimal. Checks were made on the order of patients being randomised and records were kept of any unblinding requests that were made by sites.

Any unblinding, intentional or unintentional, will be reported. The number and percentage of patients unblinded prior to database lock will be reported for each treatment group and the reason as to why they were unblinded will be reported. The denominator used to calculate the percentages is the number of participants that received any dose.

13 Patient groups for analysis

The principle of intention-to-treat, as far as is practically possible, will be the main strategy of the analysis adopted for the primary outcome and all the secondary outcomes. These analyses will be conducted on all patients randomised to the treatment groups who continued to require sedation post randomisation. Any patients that were sedated with an alternative to the allocated drug (clonidine or midazolam) or crossed over onto the other treatment arm will be included in the primary analysis in the treatment groups they were originally randomised. Patients that withdrew consent for trial continuation will contribute outcome data up until the point of withdrawal unless the patients' parents/guardians specifically request that the data are not to be used (see section 5.3.3 of the SLEEPS trial protocol).

As this is an equivalence trial, a per-protocol population (PP) will also be employed to mirror the ITT population but exclude any patients defined as having a major protocol deviation (see section 14). The planned PP analysis will be applied to the primary outcome only.

All patients who received at least one dose of intervention will be included in the safety analysis dataset. Patients will be included in the treatment group they actually received meaning that if a patient crossed over to another group for some reason they would contribute safety data to this group instead of, or in addition (if less than 12 hours* has gone by from last administration) to, their randomised group.

The membership of each analysis set will be determined and documented and reasons for participant exclusion will be given prior to the blind being broken and the randomisation lists being requested.

*12 hours was determined by doubling the half life of clonidine.

14 Protocol deviations

The table (given in Appendix B) lists potential deviations of important protocol specifications, including eligibility criteria, treatment regimens and study assessments. Protocol deviations are classified prior to unblinding of treatment. The number (and percentage) of patients with major and minor protocol deviations will be summarised by treatment group with details of type of deviation provided. The patients that are included in the ITT analysis data set, as defined in Section 13, will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

All protocol deviations will be defined and signed-off using ST001TEM03 Protocol deviations and population exclusions template associated with the Statistical Analysis Plan and Reporting SOP prior to unblinding.

15 Description of safety outcomes

15.1 Adverse reactions/events

ARs/SAEs are captured on the CRFs as free-text. These events are categorised with Chief Investigator input and subsequently signed off by Chief Investigator once complete, prior to unblinding the database.

All adverse reactions (ARs) and serious adverse events (SAEs) reported by the clinical investigator will be presented. The number and percentage of patients experiencing each categorised AR/SAE will be presented for each treatment group categorised by severity. For each patient, only the maximum severity experienced of each type of AR/SAE will be displayed. The number of events of each categorised AR/SAE will also be presented for each treatment group. No formal statistical testing will be undertaken. The safety population will be used for these summaries.

Each SAE has an ‘initial report’ done. If the SAE has not yet been resolved the ‘resolved date’ is left blank. Later, a ‘follow-up report’ or a ‘final report’ captures the ‘resolved’ date. All of the other SAE information recorded on the CRF is exactly the same as for the previous report(s). Therefore, the latest report will be taken and presented as the line listings.

15.2 Any other safety signs

The following are the seven safety procedures listed in the SLEEPS protocol:

1. Heart Rate
Heart Rate was 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 was recorded 6 hourly for 5 days following treatment cessation or until discharge, whichever occurs soonest. Heart rate was taken to help the research nurses on PICU to identify any cases of rebound hypertension. Any cases of rebound hypertension are recorded on the AR/SAE forms. This heart rate data will not be summarised or presented but rebound hypertension will be as per section 17.17.

2. Blood pressure
Blood pressure was recorded by standard PICU equipment either invasively through an arterial cannula or non invasively with a standard sphygmanometer. Blood pressure was 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 was recorded 6 hourly for 5 days following treatment cessation or until discharge, whichever occurs soonest. Blood pressure was also taken to help the research nurses on PICU to identify any cases of rebound hypertension. Any cases of rebound hypertension are recorded on the AR/SAE forms. This blood pressure data will not be summarised or presented but rebound hypertension will be as per section 17.17.

- An additional check will be performed for each patient to identify blood pressures following trial treatment cessation that are 20% greater than the highest blood pressure recorded whilst the patient was on trial treatment as this would be regarded as abnormal. Any cases identified will be checked against recorded ARs/SAEs of rebound hypertension. For those cases where no ARs/SAEs of rebound hypertension are recorded these will be queried with site to see if a possible case of rebound hypertension has been missed.

3. AE assessments
All ARs and SAEs will be reported as written in section 15.1.

4. Withdrawal symptoms
This 11 descriptors assessment for withdrawal symptoms is a secondary outcome so will be analysed and reported as written in section 17.18.

5. Fluid balance

A total of fluid in and out for each 24 hour period was recorded as per in-house fluid balance regimens. Total input included all maintenance fluids, blood products, infusion pumps etc and the fluid out measurement included all measurable secretions (urine, net nasogastric losses, drains, blood loss etc). Fluid balance (total fluids in, urine out and total fluids out) was recorded daily during trial treatment. Daily urine output is a secondary outcome so will be analysed and reported as written in section 17.11.

Fluid balance will be calculated (total fluid in - total fluid out) for each 24-hour period and then averaged over number of days for each patient. This will then be averaged over all patients within each treatment group. If the data appear to be normal the summary measures of mean, SD and range will be presented for each treatment group.

If the data appear to be skewed (i.e. non-normal) the summary measures of median, IQR and range will be presented for each treatment group.

6. Clinical Laboratory

Clinical laboratory (blood biochemistry and urinalysis) measurements are secondary outcomes so will be analysed and reported as written in section 17.13.

7. Ventilated days

The number of ventilated days was recorded for each patient. This is recorded on the 'End of study' CRF. A frequency table will be presented for the total number of days a patient was ventilated split by treatment group.

16 Analysis of primary efficacy outcome

See section 9.1 for the definition of primary outcome and how it was collected.

The COMFORT score assessment is an overall measure/impression of how the patient has been over the past hour. An occurrence of a procedure/intervention is recorded on the 'during trial treatment PICU patient bedside days 1-8' CRF under 'additional analgesia/sedation given' along with the reason for the additional analgesia.

Trial treatment began (*TST* – trial start time) with the loading dose and this was infused during the first hour of trial treatment and the maintenance rate was reached during the second hour. These two hours will be ignored in the calculation of the

primary outcome so 2 hours will be added onto the *TST* and this will be taken to be the *NTST* (new trial start time).

Patients may not necessarily begin the loading dose of the trial treatment on the hour so to account for this a weighting of '(60-*x)*/60' where *x* is the number of minutes into the first hour following the *NTST* will be applied to this period. For example, a *NTST* of 1:35 will be given a weighting of (60-35)/60=25/60. See percentage of time spent adequately sedated (*PoTAS*) formula later in this section for deails of using the weights.

The trial treatment cessation time (*TTCT*) was recorded at the end of the 'during trial treatment PICU patient bedside days 1-8' CRF and also at the beginning of the '24 hours following trial treatment cessation patient bedside follow-up day 1' CRF (if the patient moved straight to the ward afterwards this CRF does not record the *TTCT* again).

TTCT recorded on the 'during trial treatment PICU patient bedside days 1-8' CRF is considered the primary data source as this is deemed more likely to be correct as the nurses will be recording the *TTCT* on this CRF straight away. This impacts on agreement or missing data between CRFs as below:

- *TTCT* agreement between CRFs
  A check will be carried out that the *TTCT* on both the 'during trial treatment PICU patient bedside days 1-8' CRF and the '24 hours following trial treatment cessation patient bedside follow-up day 1' CRF (if applicable) agree. If they are still different following querying with site the *TTCT* from the 'during trial treatment PICU patient bedside days 1-8' CRF will be taken.

- Missing *TTCT*
  1. *TTCT* missing from the 'during trial treatment PICU patient bedside days 1-8' CRF:
     If the *TTCT* is missing from this CRF and cannot be retrieved from querying with site then the *TTCT* on the '24 hours following trial treatment cessation patient bedside follow-up day 1' CRF will be taken.
  2. *TTCT* missing from 24 hours following trial treatment cessation patient bedside follow-up day 1' CRF:
     If the *TTCT* is missing from this CRF the *TTCT* on the 'during trial treatment PICU patient bedside days 1-8' CRF will be taken.
  3. *TTCT* missing from both CRFs:
     If the *TTCT* is missing from both CRFs or the patient moved straight to the ward then the time of the last observed COMFORT score time point will be taken as the *TTCT*.
- *TTCT* to take

- For patients that have a recorded *TTCT* on the hour, this will be taken to be the *TTCT*.
- For patients that have a recorded *TTCT* part way through an hour the COMFORT score for that hour will be given a weighting of '*x*/60' where *x* is the number of minutes into the final hour the *TTCT* is. For example, a *TTCT* of 6:20 will give a weight of 20/60 for the final COMFORT score. See the formula for percentage of time spent adequately sedated (*PoTAS*) below.

Any COMFORT scores recorded after the defined *TTCT* on the 'during trial treatment PICU patient bedside days 1-8' CRF will not be included in analyses.

COMFORT scores will be eligible to be included in the primary outcome calculation if their times taken were between the *NTST* and *TTCT*. All patients who completed the loading dose and maintenance period will be included. Any randomised participants not able to contribute data will be listed.

An adequately sedated indicator variable *AS_ind* will be created for each COMFORT score (*CS*) taken defined as

$$AS\_ind = \begin{cases} 1 \; where \; 17 \leq CS \; \leq 26 \\ 0 \; where \; CS < 17 \; or \; CS > 26. \end{cases}$$

i.e. a COMFORT score that was within the range of adequate sedation (17 to 26) is given a '1' for *AS_ind* and a COMFORT score that was outside this range is given a '0'. Hours that only one COMFORT score was taken will be given a weighting (*Wt*) of '1.0'. Hours that *x* COMFORT scores were taken (where *x*>1) will be given a weighting of '1/*x*', so for example, if three COMFORT scores were taken within an hour their weighting will be '1/3' each.

The percentage of time spent adequately sedated (*PoTAS*) can then be calculated per patient as:

$$PoTAS = \left(\frac{sum \; of \; the \; (AS\_ind \; \times Wt)}{sum \; of \; all \; the \; Wt}\right) \times 100\%.$$

Any hours where a COMFORT score is missing will not count towards the analysis and i.e. not included in the numerator or denominator in the calculation above. Occurrences of missing COMFORT scores are likely to be minimal. Methods for handling missing COMFORT score data is discussed in section 18 'Analysis of missing data'. The number of patients with 1 or more intermittent missing COMFORT scores will be reported.

Next, an adequately sedated binary value (*AS*) can then be created for each patient defined by:

$$AS = \begin{cases} 1 \; where \; PoTAS \geq 80\% \\ 0 \; where \; PoTAS < 80\%. \end{cases}$$

The proportion of patients adequately sedated per treatment group (*PO_trt_grp*) can then be calculated:

$$PO\_(trt\_grp) = \left(\frac{sum\ of\ AS}{number\ of\ patients\ in\ group}\right).$$

The primary outcome for SLEEPS is testing that clonidine and midazolam are equivalent in terms of efficacy. A two-group large-sample normal approximation test of proportions using the two one-sided tests (TOST) for equivalence analysis (Schuirmann 1987[5]) using the Wald method will be used. The TOST approach includes a right-sided test for the lower margin δ_L and a left-sided test for the upper margin δ_U testing at one-sided 0.025 significance levels. The overall *p*-value is taken to be the larger of the two *p*-values from the lower and upper tests.

The null hypothesis for the equivalence test of the difference between two proportions is:

$H_0 : p_1 - p_2 \leq -\delta_L \quad \text{or} \quad p_1 - p_2 \geq \delta_U$

versus the alternative:

$H_a : \delta_L < p_1 - p_2 < \delta_U$

where δ_L is the lower margin and δ_U is the upper margin. Rejection of the null hypothesis indicates that the two binomial proportions are equivalent. The sample size calculations for SLEEPS use a ±15% (δ_L=-15%, δ_U=15%) equivalence margin.

The test-based confidence limits for the difference in proportions using the Wald method are computed as separate standard errors for the lower and upper margin tests. In this case, the test-based confidence limits are computed by using the maximum of these two standard errors. The confidence limits have a confidence coefficient of $100(1-2\alpha)$% (Schuirmann 1999[6]) so with our one-sided 0.025 significance levels a 95% confidence interval will be computed.

If the TMG decides there is an imbalance in the baseline characteristics between the two treatment groups (through 'eyeballing' of distribution rather than formal significance testing) or if there are any factors that are deemed to be confounders then logistic regression will be used for the primary outcome analysis instead including baseline characteristics and strata as covariates.

The total number of hours sedated will be calculated for each patient (*TTCT-NTST*) and summarised (mean, SD and range if data are normal; median, IQR and range if data are skewed) and presented for each treatment group. Reason for end of sedation will be summarised for all patients included in the primary analysis. Those

patients that had multiple reasons for end of sedation will be included within each catagory.

The proportion of time spent inadequately sedated will be calculated for each patient (number of hours inadequately sedated/(*TTCT-NTST)*) and summarised (mean, SD and range if data are normal; median, IQR and range if data are skewed) and presented for each treatment group.
The proportion of time spent over sedated will be calculated for each patient (number of hours spent over sedated/(*TTCT-NTST)*). This will be summarised (mean, SD and range if data are normal; median, IQR and range if data are skewed) and presented for each treatment group.

The proportion of time spent under sedated will be calculated for each patient (number of hours spend under sedated/(*TTCT-NTST)*). This will be summarised (mean, SD and range if data are normal; median, IQR and range if data are skewed) and presented for each treatment group.

The proportion of time spent inadequately sedated for each patient will be calculated as the sum of the proportions of time spent over and under sedated.

The number and percentage of patients per group that were adequately sedated (1-proportion of time spent inadequately seadted) ≥80% of the time will be presented. The difference in proportions will be given along with the 95% confidence interval using the TOST approach and the associated TOST p-value.

A per-protocol analysis will be carried out following the same methodology as for the primary analysis using the per-protocol population.

A sensitivity analysis will be performed to include the patients that were not included in the primary analysis because they did not fully complete the loading dose and two hour maintenance period. They will be assumed to be not adequately sedated i.e. *AS*=0. The per-protocol analysis and sensitivity analyses will test the robustness of the primary complete-case analysis.

See section 18 for sensitivity analyses of missing data.

17 Analysis of secondary efficacy outcomes

The SLEEPS trial protocol states the secondary objective is “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”. Therefore, the secondary outcomes are testing for superiority rather than equivalence like for the primary outcome.

The null hypothesis for each secondary outcome (in which statistical tests are being performed) will be that there is no difference in outcome between the clonidine and midazolam treatment groups. The alternative hypothesis is that there is a difference between the two treatment groups.

The protocol states that skewed continuous data will be log transformed. However, due to the substantially reduced sample size any skewed continuous data will be summarised with median, IQR and range.

17.1 Percentage of time spent adequately sedated secondary efficacy endpoint

The percentage of time spent adequately sedated will be calculated for each patient using:

$$PoTAS = \left(\frac{sum\ of\ the\ (AS\_ind\ \times Wt)}{sum\ of\ all\ the\ Wt}\right) \times 100\%,$$

where *AS_ind* and *Wt* are defined in section 15.

If the data appear to be normal the summary measures of mean, SD and range will be presented for each treatment group. The difference in means with 95% confidence intervals will be presented along with the *p*-value for a two-sample *t*-test for a difference in means.

If the data appear to be skewed (i.e. non-normal) the summary measures of median, IQR and range will be presented for each treatment group. The difference in medians with 95% confidence intervals will be presented. The difference in medians will be calculated using the Hodges-Lehman estimate with the corresponding Moses distribution-free 95% confidence intervals. The *p*-value for a non-parametric two-sample Mann-Whitney test for a difference in medians will be presented.

17.2 Time to reach the maximum permitted dose of sedation

The maximum permitted dose of sedation is as follows:

- <10kg strata: 0.2 ml/kg/hr
- 10-25kg strata: 0.16 ml/kg/hr
- >25-50kg strata: 0.04 ml/kg/hr.

These data are recorded on the CRF as mls/hr so to standardise for each patient these data measurements need to be divided by the patients' weights at trial entry. At trial entry the patients' weights are recorded as either actual or formula (if actual cannot be measured at the time). This is the weight used to calculate dose and will

therefore be used in these calculations (see section 9.2 secondary outcome 2 for details).

For each patient the time to reach the maximum permitted dose of sedation is calculated by subtracting the date and time the maximum dose of sedative was reached from the date and time of the end of the maintenance dose (i.e. 2 hours after treatment began, this will be calculated as defined for the primary efficacy analysis). For participants that did not reach the maximum permitted dose the time on sedation will be calculated as (*TTCT-NTST*). A censoring indicator, *sedative_max*, will be created for each trial participant as below:

$$sedative\_max = \begin{cases} 1 \; if \; max \; permitted \; dose \; reached \\ 0 \; if \; max \; permitted \; dose \; notreached. \end{cases}$$

If there were more than one recording of sedative dose within the hour that the maximum permitted dose of sedation was reached the final hour in the calculation will be counted as $\frac{60x}{y}$ minutes where x is the numbered measurement taken within that final hour and y is the total number of measurements taken within that final hour.

Time to reach maximum permitted dose of sedation will be calculated for each patient.

The outcome data will be compared across treatment groups using Kaplan-Meier curves and the *p*-value from a log-rank test with relative effects of treatments summarised using median times with 95% confidence intervals obtained from the Kaplan-Meier plots, and hazard ratios with 95% confidence intervals. In addition, 25% and 75% quartiles with 95% confidence intervals obtained from the Kaplan-Meier analysis will be presented.

17.3 Time to reach the maximum permitted dose of morphine

The maximum dose of permitted morphine is 3 mls/hour for all patients in the trial regardless of weight.

For each patient the time to reach the maximum permitted dose of morphine is calculated by subtracting the date:time the maximum dose of morphine was reached from the date:time of the end of the maintenance dose i.e. 2 hours after treatment began (*NTST* as shown how to calculate in section 16). For participants that did not reach the maximum permitted dose the time on sedation will be calculated as (*TTCT-NTST*). A censoring indicator *morphine_max* will be created for each trial participant as defined below:

$$morphine\_max = \begin{cases} 1\ if\ max\ permitted\ dose\ reached \\ 0\ if\ max\ permitted\ dose\ notreached. \end{cases}$$

If there were more than one recording of morphine dose within the hour that the maximum permitted dose of morphine was reached the final hour in the calculation will be counted as $\frac{60x}{y}$ minutes where x is the numbered measurement taken within that final hour and y is the total number of measurements taken within that final hour.

Time to reach maximum permitted dose of morphine will be calculated for each patient.

The outcome data will be compared across treatment groups using Kaplan-Meier curves and the *p*-value from a log-rank test with relative effects of treatments summarised using median times with 95% confidence intervals obtained from the Kaplan-Meier plots, and hazard ratios with 95% confidence intervals. In addition, 25% and 75% quartiles with 95% confidence intervals obtained from the Kaplan-Meier analysis will be presented.

17.4 Profile in rise of daily cumulative sedative infusion

These data are recorded on the CRF as an infusion rate mls/hr so to standardise for each patient these data measurements need to be divided by the patients' weights at trial entry. A cumulative summary of sedative dose will be calculated for each hour per patient. The new treatment start time (*NTST*) will be used as the start time. The first and last hours that a patient has sedative data, regardless of the exact time they started/finished treatment within those hours, will be counted as whole hours for the purposes of this analysis. If there were more than one recording of sedative dose within an hour, the mean of all doses taken within that hour will be calculated (and added to the previous cumulative total) and the measurement time will again be one hour. As the dose data are recorded as rates and there is no record of what time within the hour the doses were changed, taking the mean for the hour is considered a suitable conservative approach. Mean profile plots and individual plots by treatment groups will be presented. 1-standard error bars will be displayed for each hour on the mean profile plots. A longitudinal mixed models analysis will be performed using the assumption of sphericity. The model will include a treatment*time interaction variable. The cumulative sedative least squares means (with standard errors) for each treatment group will be presented along with differences of least square means, 95% CI and corresponding p-value.

17.5 Profile in rise of daily cumulative morphine infusion

These data are recorded on the CRF as an infusion rate mls/hr and do not need standardising for each patient based on their weight at trial entry like for sedative. A

cumulative summary of morphine dose will be calculated for each hour per patient. The new treatment start time (*NTST*) will be used as the start time. The first and last hours that a patient has morphine data, regardless of the exact time they started/finished treatment within those hours, will be counted as whole hours for the purposes of this analysis. If there were more than one recording of morphine dose within an hour, the mean of all doses taken within that hour will be calculated (and added to the previous cumulative total) and the measurement time will again be one hour. As the dose data are recorded as rates and there is no record of what time within the hour the doses were changed, taking the mean for the hour is considered a suitable conservative approach. Mean profile plots and individual plots by treatment groups will be presented. 1-standard error bars will be displayed for each hour on the mean profile plots. A longitudinal mixed models analysis will be performed using the assumption of sphericity. The model will include a treatment*time interaction variable. The cumulative morphine least squares means (with standard errors) for each treatment group will be presented along with differences of least square means, 95% CI and corresponding p-value.

17.6 Maximum permitted dose of sedative reached

These data are recorded on the CRF as mls/hr so to standardise for each patient these data measurements need to be divided by the patients' weights at trial entry. The indicator variable (*sedative_max*) defined in section 17.2 will be used to determine whether the maximum permitted dose of sedative had been reached or not:

The data will be summarised by the number (and percentage) of patients that reached the maximum permitted dose of sedative by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value.

17.7 Maximum permitted dose of morphine reached

The indicator variable (*morphine_max*) defined in section 17.3 will be used for each patient to determine whether the maximum permitted dose of morphine had been reached or not:

The data will be summarised by the number (and percentage) of patients that reached the maximum permitted dose of morphine by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value.

17.8 Fall in blood pressure judged by clinician to require intervention

The number (and percentage) of patients to have at least one occurrence of a fall in blood pressure judged by clinician to require intervention, as recorded on the 'retrospective during trial treatment days 1-8' CRF, will be presented by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value.

A frequency table will be presented for the total number of days a patient had a fall in blood pressure judged by clinician to require intervention split by treatment group. A Cochran-Armitage trend test will be performed and *p*-value presented.

17.9 Increased inotropic support required in 1st 12 hours after randomisation

The number (and percentage) of patients that had increased inotropic support in the first 12 hours after randomisation, as recorded on the 'retrospective during trial treatment day 1' CRF, will be presented by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value. It is anticipated that there will be some missing data for some of the earlier patients recruited into the trial because this question was only added to the CRF partway through the trial. At the end of the trial data management will contact sites to see if this data can be obtained from patient notes/charts. A complete-case analysis approach will be undertaken.

17.10 Supplementary analgesia required during sedation

Supplementary analgesia required during sedation is defined as any sedation, analgesia or muscle relaxants given for "loss of sedation control". Further information on collection of this is described in section 8.10. The start time for outcome will be the treatment start time (*TST*) to include any analgesias recorded during the loading dose.

The number (and percentage) of patients to have at least one instance where they required supplementary analgesia during sedation will be presented by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of

the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value.

A frequency table will be presented for the total number of instances a patient required supplementary analgesia during sedation split by treatment group. Multiple recordings of the same analgesic within an hour will be counted as one 'instance'. A Cochran-Armitage trend test will be performed and *p*-value presented.

A frequency table will be presented for each instance specific analgesias were taken as number of patients (with number of events). The same table will be presented but split by reason the analgesias were needed and by treatment group. For the specific analgesias and analgesias split by reason summary, multiple recordings of the same analgesic within an hour will be counted as multiple events.

17.11 Daily urine output

Measurements of total fluids in, urine out and total fluids out were taken approximately hourly and patients were on trial treatment for a period of time up to 7 days. As the treatment times were different for all patients the daily urine output will be standardised to get a rate per hour (ml/hour). This will be calculated for each patient using:

$$urine\_rate\_per\_hour\ (ml/hour) = \frac{sum\ of\ all\ urine\ output\ (ml)}{total\ time\ on\ trial\ treatment\ (hours)}.$$

These will then be averaged across all patients within each treatment group. Summaries of urine rate per day (*urine_rate_per_hour* x 24) will also be presented.

These measurements were taken approximately hourly so missing data will be difficult to spot. For example, if a measurement is taken at 01:00 and and the next at 02:45, we wouldn't know whether a measurement was taken at 02:00 or not. Therefore, it will be assumed that the measurements taken will reflect all the fluids in/urine out/total fluids out since the previous measurement taken.

If the data appear to be normal the summary measures of mean, SD and range will be presented for each treatment group. The difference in means with 95% confidence intervals will be presented along with the *p*-value for a two-sample *t*-test for a difference in means.

If the data appear to be skewed (i.e. non-normal) the summary measures of median, IQR and range will be presented for each treatment group. The difference in medians with 95% confidence intervals will be presented. The difference in medians will be calculated using the Hodges-Lehman estimate with the corresponding Moses distribution-free 95% confidence intervals. The *p*-value for a non-parametric two-

sample Mann-Whitney test for a difference in medians will be presented. The differences in means/medians will only be performed with corresponding *p*-value presented on the 'average daily output' to reflect the title of the outcome.

Fluids in/out will be further summarised as described in section 15.2.

17.12 Treatment failure

Treatment failure, as recorded on the CRF under reason for withdrawal, 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 occurring within any one 12 hour period during trial treatment

* 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).

The number (and percentage) of patients to have a treatment failure will be presented by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value.

17.13 Blood biochemistry and urinalysis

The data for blood biochemistry (sodium, potassium, chloride, urea, creatinine, bilirubin, ALT, AST and alkaline phosphatase) is collected at baseline and also taken once daily during trial treatment. The data for urinalysis (urea and creatinine) is taken once daily during trial treatment. Patients are on trial treatment for a period of time up to 7 days. For each blood biochemistry and urinalysis (lab data) variable, if a measurement taken is below a certain threshold, say x, for that instrument used to detect the value, it is recorded on the database as '$< x$'. To take this into account, the analyses listed below will be calculated three times assuming the following:

1. Taking the '$< x$' values to be 0.
2. Taking the '$< x$' values to be $x/2$.
3. Taking the '$< x$' values to be x.

A summary table will be presented showing the mean, SD and range (if data are normal) or the median, IQR and range (if the data are skewed) for each blood biochemistry/urinalysis variable for each day split by treatment group. The numbers of patients (*n*) that reached each time point (day) will also be given. For patients

available at each follow up time point change from baseline summaries will also be presented.

For each blood biochemistry/urinalysis (lab data) variable, the number (and percentage) of participants who have at least one abnormal result that was not expected for their condition will be presented by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value.

17.14 Urinary concentration of gamma glutamyl transpeptidase (Bristol only)

The PK/PD sub-study at the Bristol site did not go ahead as planned so these data were not collected and therefore is unable to be analysed.

17.15 Urinary concentration of alkaline phosphatase (Bristol only)

The PK/PD sub-study at the Bristol site did not go ahead as planned so these data were not collected and therefore is unable to be analysed.

17.16 Time from stopping all sedation to being fully awake (determined by a sustained** score of 4 on the alertness category of the COMFORT score)

** Sustained for 2 hours or more

Details of how to get the *TTCT* are given in section 16.

For those patients that have two consecutive alertness scores of 4 or 5, i.e. fully awake, the time of the first score will be taken to be the awake time. The number (and percentage) of patients to be fully awake will be presented by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value.

This outcome will be calculated for each child as:

$$awake\_time\_length\ (hours) = awake\ time - TTCT.$$

The *awake_time_lengths* will be compared across treatment groups using Kaplan-Meier curves and the *p*-value from a log-rank test with relative effects of treatments

summarised using median times with 95% confidence intervals obtained from the Kaplan-Meier analysis, and hazard ratios with 95% confidence intervals. In addition, 25% and 75% quartiles with 95% confidence intervals obtained from the Kaplan-Meier analysis will be presented. Patients that were fully awake when the trial treatment was stopped moved straight to the ward for follow-up. Any patients with no post-treatment cessation follow-up data will be censored at their *TTCT* and thus have an *awake_time_length* of zero. Patients with a final alertness score of 4 or 5 collected but do not have a score of 4 or 5 for the previous hour will be censored at this final hour.

Two sensitivity analyses will be performed to include the patients that have a final alertness score of 4 or 5 collected but do not have a score of 4 or 5 for the previous hour.

(1) Best-case: Classing patients with a single final alertness score of 4 or 5 as “fully awake”. This assumes that these patients were fully awake and this is the reason why no more final alertness scores were taken.
(2) Worst-case: Classing patients with a single final alertness score of 4 or 5 as “ not fully awake”.

The number (and percentage) of patients to be fully awake will be presented by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher’s exact test will be used instead to obtain the *p*-value.

17.17 Rebound hypertension

The number (and percentage) of participants who have at least one instance of rebound hypertension will be presented by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher’s exact test will be used instead to obtain the *p*-value.

A frequency table will be presented for the total number of instances a patient had rebound hypertension split by treatment group.

The number (and percentage) of patients experiencing rebound hypertension as reported as an AR will be presented for each treatment group categorised by severity. This will be reported under section 15.1.

The safety population defined in section 13 will be used for the analysis of this outcome.

17.18 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)

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)[7] (Appendix B of the protocol). At each assessment time point the symptoms were logged in the chart and rated as:

0 = None
1 = Mild (does not interfere with routine activities)
2 = Moderate (interferes with routine activities)
3 = Severe (impossible to perform routine activities).

If any abnormal behaviour was observed that were not listed then this was specified in the "Other" row. Assessment of withdrawal symptoms began when sedation ceased.

The average daily total score will be calculated for each patient by summing across the 11 defined withdrawal symptoms and then divided by the total number of assessments taken that day. Any assessments with missing observations for any of the 11 withdrawal symptoms will not be included in the calculations. Sensitivity analyses will be conducted to include the assessments with missing observations:

(1) Best-case: Missing observations assumed to be '0=None'
(2) Worst-case: Missing observations assumed to be '3=Severe'.

For the main and sensitivity analyses, the average daily total score will be presented by treatment group.

If the data appear to be normal the summary measures of mean, SD and range will be presented for each treatment group. The difference in means with 95% confidence intervals will be presented along with the *p*-value for a two-sample *t*-test for a difference in means.

If the data appear to be skewed (i.e. non-normal) the summary measures of median, IQR and range will be presented for each treatment group. The difference in medians with 95% confidence intervals will be presented. The difference in medians will be calculated using the Hodges-Lehman estimate with the corresponding Moses distribution-free 95% confidence intervals. The *p*-value for a non-parametric two-sample Mann-Whitney test for a difference in medians will be presented.

An indicator variable will be created to show whether routine activities have been affected at all:

$$routine\_activities\_effected = \begin{cases} 1 \; if \; at \; least \; one \; of \; the \; 11 \; withdrawal \; symptoms \; scored \; a \; 2 \; or \; 3 \; on \; any \; day \\ 0 \; if \; all \; of \; the \; 11 \; withdrawal \; symptoms \; scored \; a \; 0 \; or \; 1 \; for \; all \; days. \end{cases}$$

Any assessments with missing observations for any of the 11 withdrawal symptoms will not be included in the calculations. Sensitivity analyses will be conducted to include the assessments with missing observations:

(1) Best-case: Assessments with missing observations assumed to have routine activities not effected i.e. *routine_activities_effected*=0.
(2) Worst-case: Assessments with missing observations assumed to have routine activities effected i.e. *routine_activities_effected*=1.

For the main and sensitivity analyses , the number (and percentage) of participants to have their routine activities effected in some way will be presented by treatment group. Risk ratios will be computed along with 95% confidence intervals. Also, chi-squared tests will be performed with the *p*-values being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value.

The "Other" category will be summarised descriptively as line listings for each patient per day grouped by treatment.

17.19 Withdrawal symptoms requiring clinical intervention (to be recorded until 5 days following trial treatment cessation or until discharge, whichever is soonest)

The number (and percentage) of patients that had withdrawal symptoms requiring clinical intervention, as recorded on the '24 hours following trial treatment cessation patient bedside follow-up day 1', 'PICU post-treatment follow-up days 2-5' and 'ward post-treatment follow-up days 1-5' CRFs, will be presented by treatment group. A risk ratio will be computed along with a 95% confidence interval. Also, a chi-squared test will be performed with the *p*-value being presented. If any of the cells of the 2x2 contingency table have expected counts <5 then Fisher's exact test will be used instead to obtain the *p*-value.

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

ARs are captured on the AR CRF. There are three pre-defined categories:

1. Unexpected hypotension that requires intervention
2. Bradycardia that requires intervention
3. Hypertension following cessation of trial treatment

Any other ARs are captured as free-text. SAEs are captured on the SAE CRF as free-text. Those ARs/SAEs recorded as free text will be categorised with Chief Investigator input and subsequently signed off by Chief Investigator once complete.

All adverse reactions (ARs) and serious adverse events (SAEs) reported by the clinical investigator will be presented as categorised, identified by treatment group. The number (and percentage) of patients experiencing each categorised AR/SAE will be presented for each treatment group categorised by severity. For each patient, only the maximum severity experienced of each type of AR/SAE will be displayed. The number (and percentage) of occurrences of each categorised AR/SAE will also be presented for each treatment group. No formal statistical testing will be undertaken.

The safety population defined in section 15.1 will be used for the analysis of this outcome.

17.21 Cost per additional case of adequate sedation

The health economic analyses are being undertaken by a separate health economics team lead by Stavros Petrou. A separate health economic analysis plan has been developed and agreed and is listed in Appendix C.

18 Analyses of missing data

18.1 PELOD score

See the end of section 7.4 for details.

18.2 Primary outcome

A complete-case analysis will be performed so any patients that had no primary outcome data collected or did not complete the loading dose period will be excluded. For the included patients, any hours that have a missing COMFORT score are to be excluded from the primary analysis. Two sensitivity analyses will be performed to investigate the impact of this assumption:

(1) Best-case*: Missing COMFORT scores assumed to be within the range of adequate sedation (17 to 26) i.e. *AS_ind*=1.
(2) Worst-case*: Missing COMFORT scores assumed to be out of the range of adequate sedation (17 to 26) i.e. *AS_ind*=0.

* Patients that had no primary outcome data collected or did not complete the loading dose period will be assumed to have not been adequately sedated for at least 80% of the total evaluated time spent sedated (*AS*=0).

In addition a last observation carried forward (LOCF) sensitivity analysis will be carried out for missing data. We did consider using multiple imputation methods instead of LOCF but missing primary outcome data is likely to be minimal so feel it is acceptable to use LOCF. However, if it turns out that missing primary outcome data >10% we will use the multiple imputation approach.

These sensitivity analyses will test the robustness of the primary complete-case analysis and if the conclusions do not change we can be satisfied with the result.

18.3 Time from stopping all sedation to being fully awake

See section 17.16 for details.

18.4 Signs of withdrawal measured using a 11 point assessment for abnormal behaviour

See section 17.18 for details.

19 Setting results in context of previous research

Once the trial has been completed the results of the trial will be set in context of the existing evidence base[8] and results made vavailable for an update of the Cochrane review**.**

20 References

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21 Approval and agreement

The final SAP version should be converted to PDF and signed following the blinded review for protocol deviations and immediately prior to database lock as evidence of the analysis planned prior to unblinding of the study.

SAP Version Number being approved: _____

Trial Statistician

Name _____

Signed _____ Date _____

Senior Statistician or Head of Statistics

Name _____

Signed _____ Date _____

Chief Investigator

Name _____

Signed _____ Date _____

OR Electronic approval attached ☐

Chair of Trial Steering Committee

Name _____

Signed _____ Date _____

OR Electronic approval attached ☐

OR TSC not reviewing SAP (ensure agreement is documented) ☐

Chair of Data Monitoring Committee

Name _____

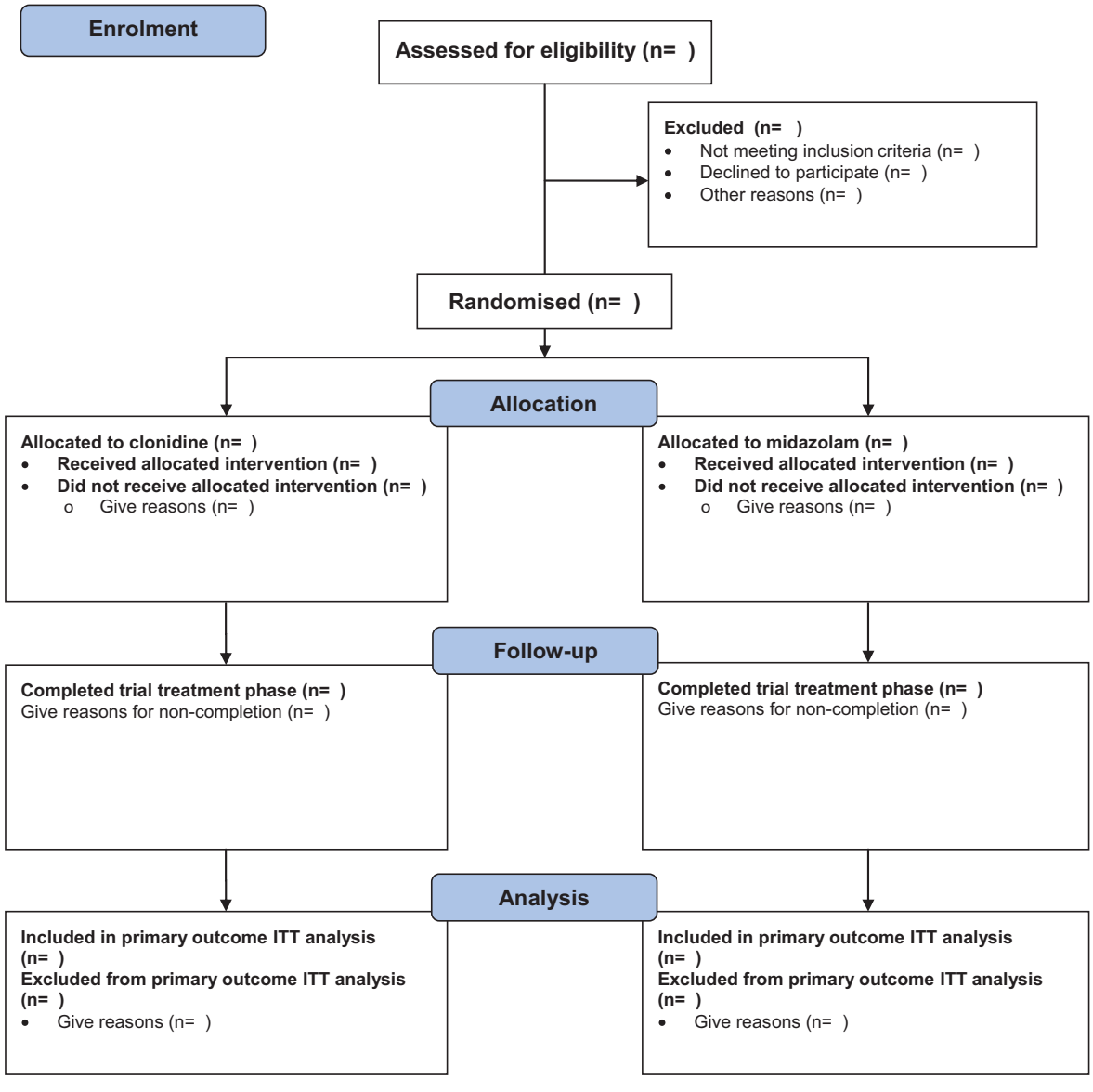
Signed _____ Date _____

OR Electronic approval attached ☐

OR IDSMC not reviewing SAP (ensure agreement is documented) ☐

Appendix A: Consort diagram

CONSORT 2010 Flow Diagram



Appendix B: Protocol Deviations Table

Note:

1. Impact refers to the impact of the potential protocol deviation on the risk of introducing bias in the defined end-points of the trial. This is generally graded as:
   - Major (in which case patients who experience this protocol deviation would generally be excluded from the "per protocol" analysis set).
   - Minor (in which case patients who experience this protocol deviation would generally be included in the "per protocol" analysis set).
2. Justification refers to the protocol-specific justification for the assessment of the impact of each potential protocol deviation.

Protocol specification	Potential deviation(s)	Impact	Justification
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.	Child aged ≥7 days but <30 days GA/CGA or >15 years but <18 years	Minor	Any violation of age criteria would be expected to be minimal (a few days rather than weeks) and there is no evidence to suggest that this would result in a different prognosis
	<7 days GA/CGA or ≥18 years	Major	Major violation of age criteria. Would result in a different prognosis
b. Admitted to PICU, ventilated and likely to require ventilation for more than 12 hours.	Not ventilated (identified by 'No' having been selected for this criterion)	Major	Violation of these criteria would result in a different prognosis
	Assumed patient would	Minor	The clinician felt that ventilation over 12 hours was likely, then this was a clinical decision and unimportant if the patient gets better quicker

Protocol specification	Potential deviation(s)	Impact	Justification
	remain ventilated for more than 12 hours but was actually ventilated for less than 12 hours		
c. Recruitment within 120 hours of arrival in PICU/ICU.	Recruitment >120 hours of arrival in PICU/ICU	Major	Violation of this criterion could result in a different prognosis but would depend on how many hours > 120 hours the child had been on PICU/ICU before recruitment. Recruitment greater than 5 days would be major in that tolerance to the drugs will already have occurred
d. Child is 50kg or less in weight	Child weighed > 50kg	Minor / Major	Violation of this criterion could result in a different prognosis but would depend on how many kgs > 50kg the child was. A weight up to 100kg would be minor with a weight over 100kg major. Decision made clinically by Chief Investigator.
e. Able to perform a COMFORT score on the child	Unable to perform a COMFORT score on the child	Major	Impossible to assess and obtain any primary outcome data / May influence effectiveness / May result in increase in ARs/SAEs
f. Adequately sedated: COMFORT score within the range of ≥17 and ≤ 26	COMFORT score <17 >26	Major	Violation of these criteria would result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs

Protocol specification	Potential deviation(s)	Impact	Justification
g. Fully informed written proxy consent	Fully informed written consent not provided or provided with inaccuracies	Major	This would have a major impact for patient rights and GCP compliance. Also, this would have a major impact on defined end-points because we could not use their data so would be missing in the analysis
EXCLUSION CRITERIA			
a. Those patients with open chests following cardiac surgery	Patient with open chest following cardiac surgery	Major	Violation of this criterion would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs
b. Those patients chronically treated for raised blood pressure	Patient chronically treated for raised blood pressure	Major	Violation of this criterion would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs
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)	Patient's current treatment with beta blockers 24 hours prior to entry	Major	Violation of this criterion would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs
d. Acute traumatic brain injury	Patient had an acute traumatic brain injury	Major	Violation of this criterion would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs

Protocol specification	Potential deviation(s)	Impact	Justification
e. Status epilepticus or active fitting (2 or more seizures regularly on a daily basis)	Patient in status epilepticus or active fitting	Major	Violation of these criteria would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs
f. Those patients requiring haemodialysis or haemofiltration	Patient required haemodialysis or haemofiltration	Major	Violation of these criteria would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs
g. Those patients requiring ECMO treatment	Patient required ECMO treatment	Major	Violation of this criterion would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs
h. Those patients with severe neuromuscular problems/impairment that you cannot perform a COMFORT score on	Patient with severe neuromuscular problems/impairment where a COMFORT score cannot be perform on	Major	Violation of these criteria would raise concerns for patient safety, may result in a different prognosis / May result in increase in ARs/SAEs / Impossible to assess and obtain any primary outcome data
i. Known allergy to either of the trial medications (clonidine, midazolam or morphine)	Patient had a known allergy to either of the trial medications	Major	Violation of these criteria would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs

Protocol specification	Potential deviation(s)	Impact	Justification
j. Current treatment with continuous or intermittent muscle relaxants.	Patient's current treatment with continuous or intermittent muscle relaxants	Major	Violation of these criteria would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs
k. Those patients known to be pregnant	Patient was pregnant	Major	Violation of this criterion would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs
l. Currently participating in a conflicting clinical study or participation in a clinical study involving a medicinal product in the last month	Patient was currently participating in a conflicting clinical study or participation in a clinical study involving a medicinal product in the month prior	Major	Violation of this criterion would raise concerns for patient safety, may result in a different prognosis / May influence effectiveness / May result in increase in ARs/SAEs
m. Previously participated in SLEEPS trial		Major	Would introduce bias
RANDOMISATION			
	Randomised to incorrect weight group (i.e. colour pack incorrect)	Major	This is highly dangerous to the patient and would likely cause an SAE

Protocol specification	Potential deviation(s)	Impact	Justification
TREATMENT REGIME	Patient randomised out of sequence	Major	Likely to introduce major bias and affect results
	COMFORT score out of range and no action taken	Major	May influence effectiveness / May result in increase in ARs/SAEs / The doses should have been modified to bring the patient back into the COMFORT score range so the patient remained out of range thus increasing the counts of hours out of range unnecessarily.
	Treatment failure had occurred and trial treatment not stopped	Major	Would affect results of primary analysis as the patient will have a greater % of time outside of acceptable range due to the extra readings after they should have been stopped
	COMFORT score between 17 and 26 and trial treatment / morphine increased/decreased incorrectly	Major	May influence efficacy assessments/ May result in increase in ARs/SAEs
	Dose increase / decrease has been recorded as the action taken, but the change in trial treatment / morphine is reflected in the following hour	Minor	Shouldn't influence effectiveness / increase in ARs/SAEs

Protocol specification	Potential deviation(s)	Impact	Justification
	COMFORT score indicates trial treatment / morphine dose increase/decrease but dose was increased/decreased by two increments or more rather than one	Major	May influence efficacy assessments / May result in increase in ARs/SAEs
	Trial treatment / morphine dose increase/decrease dose increment is either between 0-1 or 1-2 times the intended dose increment according to the trial protocol	Minor	Shouldn't influence effectiveness / increase in ARs/SAEs
	COMFORT score calculated incorrectly as being between 17 and 26 when a dose increase / decrease should have occurred	Major	May influence efficacy assessments / May result in increase in ARs/SAEs
	COMFORT score calculated incorrectly and dose decrease / increase occurred when COMFORT score actually between 17 and	Major	May influence efficacy assessments / May result in increase in ARs/SAEs

Protocol specification	Potential deviation(s)	Impact	Justification
	26 Maintenance rate calculated incorrectly therefore administered at the incorrect dose	Major	May influence efficacy assessments / May result in increase in ARs/SAEs
	Trial treatment / morphine increased/decreased rather than morphine / trial treatment	Major	May influence efficacy assessments / May result in increase in ARs/SAEs
	Dose increase / decrease made to both trial treatment and morphine when only trial treatment / morphine should have been adjusted	Major	Shouldn't influence effectiveness / increase in ARs/SAEs
	Decrease/increase of trial treatment / morphine when a dose increase/decrease was indicated	Major	Would raise concerns for patient safety. May influence efficacy assessments / May result in increase in ARs/SAEs
	Decrease/increase of trial treatment / morphine / both when NAT was needed to be	Minor	Shouldn't influence effectiveness / increase in ARs/SAEs

Protocol specification	Potential deviation(s)	Impact	Justification
	sustained for 1 hour (according to SLEEPS study flowchart v1.2)		
	Both trial treatment and morphine decreased instead of a morphine increase	Major	May influence effectiveness / May result in increase in ARs/SAEs
	Both trial treatment decreased and morphine increased instead of a morphine increase	Minor	Shouldn't influence effectiveness / increase in ARs/SAEs
	Trial treatment decreased instead of trial treatment being temporarily stopped	Minor	Shouldn't influence effectiveness / increase in ARs/SAEs
	Patient randomised following temperature deviation / unreliable temperature recording	Major	May influence effectiveness / May result in increase in ARs/SAEs
	Patient commenced trial treatment after 24 hr window following consent	Minor	Shouldn't influence effectiveness / increase in ARs/SAEs

Protocol specification	Potential deviation(s)	Impact	Justification
	Patient started both trial treatment and morphine at the same time instead of morphine followed by trial treatment 15 minutes later	Minor	Shouldn't influence effectiveness / increase in ARs/SAEs
PRIMARY OUTCOME	Missing data	Major	May influence interpretation of results

Appendix C: Health Economics Analysis Plan

THE UNIVERSITY OF LIVERPOOL

SLEEPS (Safety profiLe, Efficacy and Equivalence in Paediatric Intensive care Sedation)Trial

Health Economics Analysis Plan

Angela Boland / Stavros Petrou

May 2013

1 Health Economics Analysis Plan: SLEEPS TRIAL

1.1 Primary objective and summary of economic evaluation methods

The economic evaluation will assess the cost effectiveness of two intravenous sedative agents (clonidine versus midazolam) that are administered in the treatment of critically ill children using clinical data from the SLEEPS trial. An economic evaluation has been integrated into the design of the trial. The primary outcome of the SLEEPS trial is adequate sedation; a child is adequately sedated if s/he spends "at least 80% of total time sedated within COMFORT range of 17 to 26". This measure of effectiveness will be calculated by the medical statistics team and made available to the health economists working on the trial.

Clinical research forms (CRFs) used by the clinical team have been designed to capture the duration and intensity of care provided to each child, based on standard criteria for level of care, as well as any complications experienced. Details of the resources associated with salient clinical events will therefore be recorded. For each of the two treatment groups, adequate sedation levels will be compared and the measure of benefit used in the economic evaluation will be additional case of adequate sedation observed. Given the methodological limitations surrounding preference-based outcomes measurement in young children, outcomes will not be expressed in terms of preference-based metrics, such as the quality-adjusted life year (QALY).

The economic evaluation will be performed from an NHS hospital services perspective using NHS direct costs only; non-NHS costs will not be considered.

In the primary analysis, costs and benefits will be identified, measured and valued for each trial participant from the date and time of randomisation to 14 days post treatment cessation. An incremental cost-effectiveness analysis (CEA) will be conducted in order to calculate the incremental cost per additional case of adequate sedation observed. A range of sensitivity and a scenario analysis will be performed alongside the primary analysis.

2. Using data from the SLEEPS trialto inform Economicanalyses

2.1 Data collection, calculation and analyses

All data received by the health economists working on the economic evaluation will be reviewed carefully on receipt following data entry and cleaning by the central trial administrative team. Specifically, all unique patient identifiers and completion dates will be checked and verified. The health economists involved in the study anticipate having access to the unblinded health economics data whilst the trial is in progress; this is to ensure that data are being collected as specified in the SLEEPS protocol and related CRFs and that any data entry errors/procedures can be corrected/amended as early as possible.

Where appropriate, efforts will be made to identify and/or impute missing data. Missing NHS resource use data are often straightforward to locate. Extracts of hospital contact records are available from all trial sites, and these will be cross-checked against SLEEPS trial records to ensure that any conflicts or omissions are detected and corrected. Multiple imputation methods may be used to impute missing data and avoid biases associated with complete case analysis (Briggs 2003); however, missing data is not anticipated to represent a major problem as all data for use in the economic evaluation will be routinely collected by hospital staff using the CRFs.

2.1.1 Collection and validation of resource use data

Resource use data will be collected via the CRFs that are used by the clinical team to collect clinical effectiveness data during the trial; these forms will be the key source of significant health service resource input data whilst the trial participants attend hospital. There are ten individual CRFs per trial participant that will be used for data collection during the trial. The health economists involved in the study were consulted during the pilot and design stages of the CRFs.

The study CRFs will capture all resource use related to the child's hospital inpatient stay, including diagnosis and treatment as well as transfers between wards and hospitals. Specifically, individualised resource use will be estimated for the resources associated with each child's intervention, length of stay in paediatric intensive care unit (PICU), length of stay in high dependence unit (HDU), length of stay in general ward, duration of mechanical ventilation during the hospital admission, surgical procedures performed during the hospital admission, tests or investigations performed during the hospital admission, and resources

associated with treatment of serious adverse events (SAEs). Duration of resource use for significant resource items during the hospital admission will also be recorded.

2.1.2 Unit costs

Unit costs for resources used by children who participate in the study will be obtained from a variety of primary and secondary sources, with the majority being obtained from secondary sources. All unit costs employed will follow recent guidelines on costing health and social care services as part of an economic evaluation (Drummond 2005, NICE 2013). Where necessary, secondary information will be obtained from ad hoc studies reported in the literature. Unit costs of hospital and community health care costs will be largely derived from national sources and will take account of the cost of the health professionals' qualifications (Curtis 2012). Some costs will be valued using the NHS Reference Costs (2011-12), a catalogue of costs compiled by the Department of Health in England (Department of Health 2012). Drug costs will be obtained from the British National Formulary (BNF 2012) and MIMS (2013). All costs will be expressed in pound sterling and valued at 2011-2012 prices. None of the costs will be inflated or deflated for use in the economic evaluation. For the primary analysis, unit costs will be combined with resource volumes to obtain a net cost per trial participant covering all categories of hospital costs. All unit costs employed will follow recent guidelines on costing health care services as part of economic evaluation. The calculation of these costs will be underpinned by the concept of opportunity cost.

2.1.3 Statistical analyses and calculation of cost-effectiveness ratios

Independent-sample t-tests will be used to test for differences in resource use, costs, and number of cases of adequate sedation observed between treatment groups. All statistical tests will be two-tailed. If appropriate, multiple regression analysis will be used to estimate the differences in total cost between clonidine and midazolam groups and to adjust for potential confounders, including the covariates incorporated into the main clinical analyses. In the primary analysis, the incremental cost-effectiveness analysis ratio (ICER) of interest will be the incremental cost per additional case of adequate sedation observed.

For the economic evaluation, differences in mean costs and effects between the groups will be calculated. The ICER will be calculated as the difference in costs (ΔC) divided by the difference in number of cases of adequate sedation. The economic evaluation will estimate the cost per additional case of adequate sedation observed, and the primary analysis will follow trial participants from randomisation to 14 days post treatment cessation as this will ensure that any differences in costs or healthcare resource use that result from the intervention will be captured. Discounting of future costs or benefits will not be applied as the time horizon is less than 12 months.

Estimates of the probability of clonidine being less costly, more effective, dominant or dominated relative to standard care at different ceiling ratios will be calculated. Non-parametric bootstrap estimation will be used to derive 95% confidence intervals for mean cost differences between the trial groups and to calculate 95% confidence intervals for ICERs. The planned economic evaluation will conform to nationally agreed design and reporting guidelines and will incorporate detailed resource use and clinical effectiveness data from all subjects recruited into the trial. The proposed analytical strategy will follow the recent requirements stipulated by decision-making bodies.

Uncertainty around the conclusions about whether or not treatment is cost effective will be represented in the form of cost-effectiveness acceptability curves (CEAC). This will show the probability of the addition of treatment being cost-effective at a range of maximum values (termed ceiling ratios, Rc) that decision-makers may be willing to pay for an additional case of adequate sedation. The CEACs and the probability of treatment being cost-effective will be calculated based on the proportion of simulations with positive net benefits at a range of ceiling ratios.

2.1.4 Sensitivity and scenario analyses

A series of simple and probabilistic sensitivity analyses will be undertaken to explore the implications of uncertainty on the estimated ICER and to consider the broader issue of the generalisability of the study results. One-way sensitivity analysis will include the following parameter variations: higher per diem PICU/HDU ward cost; lower per diem PICU/HDU ward costs; use of fractions of time in estimation of total length of stay and estimation of costs from randomisation to 14 days post-ventilation cessation. A scenario analysis will also be conducted and will be undertaken from a wider NHS perspective – additional GP visit, accident and emergency and hospital re-admissions costs will be included.

A final exhaustive list of the sensitivity analyses investigated will be made available (including *post hoc*[1] analyses) and the results of all analyses conducted will be included in the final report.

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[1] Post hoc analyses comprised widening and narrowing the definition of adequate sedation from '80% of total time sedated within a COMFORT score range of 17 to 26' to 75% and 85% respectively.