Paramedic Analgesia Comparing Ketamine and MorphiNe in trauma: PACKMaN

# STATISTICAL & HEALTH ECONOMIC ANALYSIS PLAN

| | |
|---|---|
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# Contents

## 1. ADMINISTRATIVE INFORMATION

Title: Paramedic Analgesia Comparing Ketamine and MorphiNe in trauma: PACKMaN

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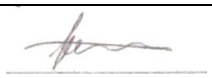
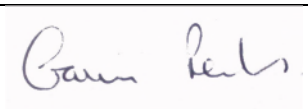
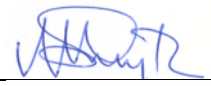
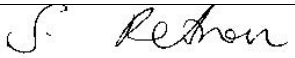
Roles and responsibility:

Signatures of:

| **Role** | **Name** | **Date** | **Signature** |
|---|---|---|---|
| Author of SAP | Felix Michelet | 14/06/2023 |  |
| Senior statistician | Ranjit Lall | 14.06.2023 |  |
| Chief Investigator | Gavin Perkins | 8/6/23 |  |
| Chief investigator | Mike Smyth | 13/06/2023 |  |
| DMC Chair | Siobhan Creanor | 25/05/2023 |  |
| Health Economist | Kamran Khan | 23/05/2023 |  |

| | | | |
|---|---|---|---|
| Senior Health Economist | Stavros Petrou | 07/06/2023 |  |

# Section 1: Summary of PACKMAN

## 1.1 General principles for the primary statistical and health economic analysis

Given the trial is funded by the National Institute for Health Research, we will adopt principles that best meet the requirements of United Kingdom decision makers. The methods of economic evaluation will therefore be guided by the National Institute for Health and Care Excellence (NICE) guide to the methods of technology appraisal[1].

## 1.2 Trial Design

This is a multi-centre, randomised, double blinded trial comparing the clinical and cost-effectiveness of ketamine and morphine for severe pain in acute traumatic injury. It is a pragmatic, phase III trial working with two large NHS ambulance trusts with an internal pilot. Participants will be followed up for 6 months. Patients will be divided into each arm with an allocation ratio of 1:1, receiving either morphine or ketamine.

The treatment intervention, ketamine, will be supplied in ampoules containing 15mg in 1ml. The control intervention, morphine, will be supplied in ampoules containing 10mg in 1 ml. The ampoules will be labelled as trial related investigational medicinal product (IMP) and will be identical regardless of whether it contains ketamine or morphine. This is so that the paramedic is not able to identify which treatment they are administering.

## 1.3 Objectives

In the PACKMaN study, the study objective will be to test the hypothesis that paramedic administered ketamine provides more effective pain relief than morphine, for patients reporting severe pain following trauma. The Sum of Pain Intensity Difference (SPID) assessed using a 0-10 numeric rating scale and time of observation will be measured to compare morphine to ketamine.

The secondary objectives of the PACKMaN trial are to assess the effects of paramedic administered ketamine or morphine on overall pain relief / patient experience, tolerability, resource used, longer term outcomes and cost effectiveness.

## 1.4 Target population

Patients that meet the following criteria are the desired population for analysis:

**Inclusion criteria**

1. Age ≥16
2. Patient reports a pain score ≥7/10 on a 0-10 NRS following acute traumatic injury
3. Intravenous (IV) or intraosseous (IO) access obtained
4. Determined by a paramedic to require IV morphine or equivalent

**Exclusion criteria**

1. Known or suspected pregnancy
2. Unable to articulate severity of pain using the 0-10 NRS
3. Lack of capacity due to a reason other than pain
4. Intravenous or intraosseous (IV/IO) ketamine or opioid analgesia immediately prior to randomisation*
5. Known contraindication to either ketamine or morphine as per the SmPC**
6. Patient declines participation
7. Known prisoner

* This criterion is intended to exclude only those patients' administered ketamine or opioids via IV/IO route immediately prior to randomisation.

**SmPC is the abbreviation for Summary of Product Characteristics

## 1.5 Outcome measures

**Primary Outcome**

Effectiveness of pain relief from randomisation to arrival at hospital as measured by Sum of Pain Intensity Difference (SPID) score (using a 0-10 numerical rating scale)

**Secondary Outcomes**

*Effectiveness of pain relief and overall patient experience from randomisation to arrival at hospital*

- Total Pain Relief (TOTPAR) score
- Time to perceptible analgesia
- Time to meaningful analgesia
- Time to peak analgesia
- Duration of analgesia
- Requirement for rescue analgesia
- Proportion of patients with a pain intensity score below 4/10 (0-10 numerical rating scale (NRS)) on arrival at hospital
- Vital signs (oxygen saturation, blood pressure, heart rate, respiration rate, Glasgow Coma Scale)
- Patient Global Impression of Change on arrival at hospital

*Incidence of side effects and adverse events*

- Airway: vomiting, aspiration, advanced airway management
- Respiratory: desaturation, need for ventilatory support
- Cardiovascular: arrhythmia, hypotension and hypertension
- Neurologic: sedation, excitatory movements, adverse behavioural reactions

- Other: nausea, allergic reaction

*Resource use*

- Ambulance job cycle time (scene arrival to arrival at hospital)
- Number of ambulance resources (technicians, paramedics, doctors and vehicles) in attendance
- Cumulative IMP doses administered
- CT scan use
- Hospital or ICU admission
- Length of stay ED, ICU, Hospital

*Longer term outcomes*

- Chronic pain using BPI-SF at 3 & 6 months from randomisation
- Health-related quality of life EQ-5D-5L and CSRI at 3 and 6 months from randomisation
- Cost-effectiveness expressed in terms of incremental cost per quality-adjusted life year (QALY) gained using EQ-5D 5L and CSRI (at 3- and 6-months post randomisation)

**Safety**

Patient adverse events listed in the secondary outcomes will be summarised and reported, these however will be exempt from reporting unless deemed serious, as they will be collected on the case report form. Other adverse events which are not related to the acute traumatic injury or are complications resulting from the IMP administration to 30 days post IMP will be reported to the PACKMaN Trial team as soon as possible and within 24 hours of the research staff becoming aware of the event.

Any change of condition or other follow-up information should be sent to the PACKMaN Trial team as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or an outcome has been reached.

The SAEs will be assessed for causality from treatment and the relationship will be classed as unrelated, unlikely to be related, possible relationship, probable relationship, or definitely related.

# Section 2: Monitoring of the PACKMAN Trial (operational and statistical)

## 2.1 Operational monitoring

### 2.1.1 Recruitment by ambulance service

Two ambulance trusts (services) have been selected to randomise patients.

Recruitment by ambulance service is summarised in Tables 1 and 2. These tables illustrate the balance of randomisation across the services and the number of patients recruited, with number of patients recruited per month.

### 2.1.2 Recruitment of patients

A consort diagram showing the flow chart of patients recruited in the trial is illustrated in figure 1.

- A detailed diagram showing the flow chart of patients from recruitment to hospital discharge will be illustrated in figure 2
- Reasons for non-enrolment will be detailed in tables 3, 4a and 4b
- A participant flow table will be included for the trial in table 5. In this diagram participant deaths and withdrawals will be summarised between hospital arrival and 3 month follow up. Between 3 month and 6 month follow up and after having reached 6 months follow up we will summarise participants death and withdrawals still, as well as those who declined consent during the follow up rate, those lost to follow and non-respondents.

### 2.1.2 Withdrawals & follow up rates

Withdrawals will be summarised using frequencies and percentages (Table 6).

There are two main levels of withdrawal: (a) withdrawal from treatment; (b) withdrawal from study.

For withdrawal from study, this may occur: (a) prior to hospital arrival; (b) from hospital arrival to discharge; (c) from discharge to 3 months; (d) from 3 months to 6 months.

The reasons for withdrawal will be noted and presented in Listing 1.

Cumulative withdrawals and deaths are summarised in tables 6 and 7.

### 2.1.3 Protocol violations and deviations

Protocol violations, with number of patients (and percentage in each arm) will be tabulated as in Table 8a and Table 8b.

Protocol deviators, with number of patients (and percentage in each arm) will also be presented as in Table 9a and Table 9b.

For each of these, we will present the number of patients who have at least one violation/deviation and the total number of violations/deviations. We will further present the details of these by each treatment arm.

### 2.1.4 Safety data

Serious adverse events and adverse events, with number of patients with at least one event (and percentage in each arm) and the total number of events will be tabulated as in Table 10 and Table 11 respectively.

Listings 2 and 3 details the description of the serious adverse event and adverse events by treatment arm.

### 2.1.5 Unblinding

Unblinding requests will be summarised by treatment arm in table 12. In this table we will detail the ambulance site that has requested the unblinding, as well as the date and further details on the unblinding.

### 2.1.6 Paramedic experience

We will also look at the trial paramedics and their experiences, but this will not form part of the main reporting of the trial and analysis.

Trial trained paramedics and participant recruits will be summarised by paramedic experience level (NQP vs band 6 paramedic) in table 13. We will also summarise the number of incidences of serious adverse events & non-compliances by paramedic experience level in frequencies and percentages. These will also be looked at by treatment arm in table 14, table 15, and table 16.

## 2.2 Statistical monitoring during the trial

### 2.2.1 Randomisation

Randomisation will be achieved by way of specially prepared, sequentially numbered treatment packs containing identical ampoules of either morphine (comparator) or ketamine (intervention). The content of the drug packs will be determined from a randomisation list prepared by the study programmer. The blinded block randomisation system will look to ensure a ratio of 1:1 control: intervention. The balance between arms at each site is handled by the ordering system that ensures a pre specified number of paired packs are delivered to each site. The block size is determined by the number of drugs in any given site batch order. Distribution of trial drug packs by the trial drug manufacturer will ensure equal proportions of morphine (comparator) and ketamine (intervention) are distributed to each participating site. Allocation will be concealed from study personnel, ambulance staff and patients.

Numbered study drug packs in a pre-randomised sequence, will be carried by participating ambulance paramedics. Randomisation will be achieved by opening the pack, the packs will not necessarily be opened in sequential order. Due to the method of randomisation, it will not be possible to stratify the randomisation. However, we will examine how factors such as, age, gender and use of alternative parenteral analgesia are distributed across treatment arms.

### 2.2.2 Adequacy of blinding

To determine the adequacy of the blinding procedure some trial paramedics have been selected to attempt to guess which treatment has been given. The trial statistician randomly selected 16 packs per site ensuring a balance across treatment arms. If one of these packs is used for a recruit, the research paramedic will get in touch with the recruiting paramedic to ask them to guess what IMP they think they administer and the reasons why they think the IMP they guessed may be the correct one. This will be done after randomisation and pain score data collection. The results from this procedure will be summarised in table 17.

### 2.2.3 Sample size

For the sample size calculation, we have used the Sum of Pain Intensity Difference (SPID) as the primary outcome measure. Our sample size is calculated to detect a 1-point difference (0-10 NRS) in the primary outcome (SPID) between morphine and ketamine. Other randomised controlled trials comparing ketamine and morphine have adopted a standard deviation of 3.0[2-5]), while our review of previous prehospital analgesia studies showed an average withdrawal rate of 14%[2,6-9]. Therefore, assuming a standard deviation of 3.0, with a clinically relevant difference of 1 point, 1:1 randomisation, a power of 90%, significance level of 5%, and withdrawal/non-response rate of 15%, we require a sample size of 446 patients.

To ensure the required sample size is achieved, we will monitor post-randomisation exclusions, withdrawals and non-responders and assess their impact on the required sample size/detectable effect size.

### 2.2.4 Non-compliance

IMP dosage compliance will be monitored. Both morphine and ketamine are controlled drugs and therefore correct IMP dosing will be important. Data Collection Form CRF02 is used to retrospectively calculate the IMP dose given based on the patient's weight and to ensure that the correct dose timing was used. Guidance on volumes and administration times are provided in the PACKMaN protocol. We will monitor that no patient received > 20ml or the patient's weight was <50kg to check the weight adjusted dose was appropriate. We will monitor any instances of an overdose or underdose.

An overdose will be defined as:

- More than 20ml IMP administered
- Further doses of IMP administered despite a pain score of 0
- IMP administered too rapidly (>10mls in first 10 mins and/or first 10mls given in less than 5 mins as this exceeds the protocol dosing schedule) in conjunction with the presence of adverse events and/or the use of midazolam/naloxone

An underdose will be defined as:

- Pain score at hospital arrival is 7 or more and the full 20ml of IMP has not been administered, with no reasonable justifications
- IMP administration period exceeds 60 mins, with no reasonable justifications provided.

As PACKMaN is a pragmatic trial, it is acknowledged that the timings of IMP dose administration will be varied given real life trauma situations and this will therefore not impact data integrity. As such, dosing times above and below the 5 mins interval stated in the protocol (for guidance purposes), are expected. IMP administration over an extended period of time is also expected. Therefore, in cases where IMP is deemed to have been given too rapidly or it is not possible to determine the IMP administration intervals or overall period, the occurrence of adverse events and/or the use of midazolam/naloxone will be used by the TMG to determine whether the event is a non-compliance. These 2 parameters will also be used to assess whether an event is a deviation, violation, serious breach or none of these.

# Section 3: Datasets used from the PACKMAN database

## 3.1 Intention to treat

All analysis will be based on '**Intention-to-treat' (ITT),** this will include all patients randomised.

An ITT analysis produces estimates as would be in the `real world' and maintains the baseline comparability achieved by the randomisation process.

The point of randomisation is defined as the time when drug pack is opened. It may be that we will have a small number of patients who are found to be ineligible before any trial drug was administered, but the pack was opened. Using Fergusson et al. (2002), criteria, we will determine if a patient needs to be excluded from the ITT population[10]. For these post-randomisation exclusions, we will assess their baseline and any other data collected (that they have agreed to) to ensure that this group is similar to the study (ITT) population and no bias has occurred in excluding these patients.

The patients will be assessed for eligibility by the paramedic upon arrival to scene. Eligible patients will be informed by the attending paramedic that they are eligible to participate in the PACKMaN study and that paramedic intends to enrol them in the study unless they prefer to receive usual treatment (morphine). Informed written consent will be obtained by research paramedics after the patient is admitted to the Emergency Department. All patients that are eligible will be analysed according to the treatment arm they were randomised to, irrespective of the treatment they received. All patients with sufficient data to calculate the primary outcome will be included in the primary analysis, from baseline, and will be included in the secondary analysis provided they offer consent/complete follow up questionnaires. Participant safety data and serious adverse event data will use the same ITT population as the primary outcome.

## 3.2 Analysis datasets

**Observed dataset**

This will comprise of all the data observed (including follow up) with missing values.

**Imputed dataset**

See section 4.4.

# Section 4: Analysis of the primary outcome and the Estimand Framework for PACKMAN (in relation to the primary outcome)

## 4.1 Primary outcome and the Estimand framework

In line with the ICH E9 (R1) addendum on Estimand and sensitivity analyses in clinical trials, the following defines the Estimand framework, in relation to the primary outcome.[11]

| **Estimand attribute** | **Description** |
|---|---|
| *Objective* | To assess the effectiveness of paramedic administered Ketamine (intervention) with Morphine (standard care) for pain relief in patients reporting severe trauma, from randomisation to arrival at hospital |
| *Treatment conditions* | Pain resulting from acute trauma injury in an emergency care setting |
| *Population* | Adults (≥ 16 years) participants, identified by the attending paramedic (pre-hospital), where an intravenous (IV) or intraosseous (IO) access can be obtained |
| *Variable (outcome)* | Sum of Pain Intensity Difference (SPID) score (using a 0-10 numerical rating scale), from randomisation to arrival at hospital.<br><br>Variables used for SPID are the patients pain score and the time at which the observation was taken.<br><br>The point of randomisation is defined as the time when drug pack is opened. Arrival at hospital is when the vehicle arrives at the ED department, not when the participant is admitted to ED. |
| *Summary measure* | The SPID is measured using a weighted sum of the scores, as shown below:<br><br>$SPID_n = \sum_{i-1}^{n} (T_i - T_{i-1}) * PID_i$<br><br>$T_i$ is the time in hours when observation *i* is taken. $PID_i$ is the difference in Pain Intensity (PI) scores from initial pain score to the pain score at time $T_i$. The SPID looks to calculate the area under the curve of pain intensity difference over time, using the trapezoidal rule. The summary statistics will be the mean (SD), together with the 95% confidence interval of the SPID for all the patients in the study.<br><br>The SPID will be summarised by treatment arms. |
| *Handling Intercurrent events* | Post-randomisation events which may affect the interpretation or occurrence of the primary outcome include: |

| | |
|---|---|
| | ICE 1: discontinuation of the allocated treatment (i.e., withdrawal from treatment not study)<br><br>ICE 2: use of rescue medication<br><br>ICE 3: non-compliance: over-dosing, or under-dosing<br><br>ICE 4: death during period from initial IMP admin to hospital arrival |
| *Strategies for handling intercurrent events* | ICE 1:<br>(a) *Treatment policy* (same as main analysis) - analysis as observed because it is unlikely that patients will be withdrawn, or treatment discontinued. Treatment discontinuation is defined as either participant is withdrawn from treatment without reason, or participant dies before hospital arrival, or participant has an adverse event that results in treatment stopping.<br>ICE 2:<br>(a) *Treatment policy* (same as main analysis) - i.e., analyse as observed data. Use of rescue medication is considered part of the treatment and we will assess the effect of the intervention, regardless of the event<br>ICE 3:<br>(a) *Principal stratum strategy* - assessing the effect of the intervention, having adjusted for the non-compliance (i.e., over-dosing/under-dosing); see below for details of analysis.<br>ICE 4:<br>(a) *Composite strategy:* using death as a composite with the primary outcome (see below for details of analysis). |

Treatment policy will result in the primary analysis

## 4.2 Primary outcome (summaries and statistical analysis)

Primary outcome data will be summarised with descriptive statistics (n, mean, standard deviation, median, interquartile range, and n of missing data). We anticipate low levels of missing data for the primary outcome at the end of the trial.

Baseline pain score will be calculated as the latest available pain measurement before initial IMP dose was administered, in the unlikely event that this baseline score is 0, the data will be classed as missing.

Results of all the statistical analysis using statistical modelling will be presented using mean (sd) and two-sided 95% confidence intervals. The primary analysis will be carried out using linear regression on an ITT population and on the observed data with adjustments for the following covariates as fixed effects:

- ambulance service
- age (<60; ≥60 years)
- gender (male, female, transgender, other, not disclosed)
- administration of intravenous paracetamol prior to randomisation (yes, no)
- weight (cutpoint on the mean/median)

Ambulance service is included as a covariate as there may be some differences in practice across sites. Age and gender are included as covariates as the groups specified can experience pain differently. Administration of IV paracetamol prior to randomisation is included as a covariate as it is an adjunctive treatment that may impact pain response. Weight is included as a covariate since different weight groups have different requirement for an adequate dose of IMP.

The secondary analysis will be the unadjusted analysis.

Model assumptions will be checked visually, for example through the use of residual plots and if necessary, hypothesis tests will be used (i.e the Anderson Darling test for checking if errors are normally distributed).

For heavily skewed data, where the standard deviation is larger than the mean, we will assess methods will accommodate for the non-normality in the data (e.g. Gamma distribution models or transformation of the data), instead of linear regression models. Descriptive statistics and results will be presented with adjusted and unadjusted models in tables 18 and 19. Hypothesis tests will be conducted at a two-sided 5% significance level and their corresponding p-value will be reported. There is no adjustment for multiple testing for the PACKMaN trial.

Graphical display of participant pain score differences over time/observations will be explored for summary of the primary outcome.

## 4.3 Primary outcome (sensitivity analyses)

The sensitivity analyses for the primary outcome will be those described above in section 4.1, around the estimand framework.[11] All the statistical analysis using statistical modelling will be presented using mean (sd) and 95% confidence intervals.

*Intercurrent event 1 (Treatment policy):*

In the case of discontinuation of treatment we will analyse the data based on the ITT population specified in section 3.1.

*Intercurrent event 2 (Treatment policy):*

In the event of rescue analgesia being used we will analyse the data based on the ITT population specified in section 3.1.

*Intercurrent event 3 (Composite strategy):*

The effect of compliance will be assessed using a complier average causal effect (CACE) analysis[12,13] will be conducted for the primary outcome and mortality. A structural mean model with the inclusion of an instrumental variable will be fitted to estimate the treatment effect among those who complied with the study drug infusion protocol. Results will be presented in tables 20-28.

*Intercurrent event 4 (Composite strategy):*

The death rate prior to completion of data collected to calculate the primary outcome is expected to be low. If there are more than 5% death affecting assessment of the primary outcome across all participants, we will use the Pocock's win-ratio method[14]. In the Pocock's win-ratio, each patient from the intervention group is compared to each patient in the standard care group (a total of *m x n* comparisons where *m* is the total number of patients in the intervention group and *n* the number of patients in the standard care group) for the mortality endpoint and then on the primary outcome. Based on which patient performs better in each pair, the group they belong to will be declared the 'winner'. This will give us the total number of winners in each group and our test statistic is based on this. In the case of the win-ratio method, the statistic is the number of winners in the intervention group divided by the number of winners in the standard care group. This approach allows us to infer if the intervention is significantly better than the standard care having considered the clinical priority i.e., treating mortality as a more important outcome than having a better primary outcome.

## 4.4 Primary outcome (imputation analysis)

Some item missingness for the primary outcome is expected, however if 2 or more pain scores are recorded for a participant the primary outcome will still be able to be calculated. Due to the nature of the data it will be difficult to judge when an item is genuinely missing or when it is clinically reasonable for a participating paramedic to not record participant pain scores. Multiple imputation is not recommended if data is missing not at random (MNAR).[15] Imputation methods were considered by the statisticians along with the trial management team and it was deemed that last observation carried forward was not suitable due to the variability of pain scores for participants. Clinically, there are also reasons for why a paramedic may not have recorded a pain score so we cannot assume that data are missing at random, therefore multiple imputation is also not possible.

Additionally, the primary outcome is calculated as the area under the curve using the pain scores of the participant, therefore imputing missing items will not improve the measurement of the primary outcome.

# Section 5: Secondary Outcomes and other data collection

## 5.1 Secondary Outcomes and data collection

| Secondary Outcomes | Definition | Mitigations |
|---|---|---|
| The Total Pain Relief (TOTPAR) | The TOTPAR is measured using a weighted sum of the scores, as shown below:<br>$TOTPAR_n = \sum_{i-1}^{n} (T_i - T_{i-1}) * PAR_i$<br><br>$T_i$ is the time in hours when observation $i$ is taken.<br><br>$PAR_i$ is the pain relief score measured as defined below on a scale of 1 to 3.<br><br>We measure minimal pain relief as 1.8 (1.7-1.9) change in pain score, much pain relief as 4.0 (3.9-4.1) and very much pain relief as 5.2 (5-5.4)[16].<br><br>Percentage changes defined as 20.3 (19-21.6), 44.4 (43.2–45.6), 56.1 (53.9–58.4) respectively[16]. | |
| Time to Perceptible Analgesia | Perceptible pain relief is defined as a 20% improvement in NRS pain score from the initial pain score[16]. The time will be taken as time of perceptible analgesia minus time of first administration. | If 20% improvement not achieved, we will score this as perceptible analgesia not achieved. |
| Time to Meaningful Analgesia | Defined as a 44% improvement in NRS pain score from initial pain score[16]. The time will be taken as time of meaningful analgesia minus time of first administration. | If 44% improvement not achieved, we will score this as meaningful analgesia not achieved. |
| Time to Peak Analgesia | Measured as the time when lowest NRS pain score, relative to initial pain score, is | |

| | | |
|---|---|---|
| | achieved minus time of first administration. | |
| Duration of Analgesia | Measured as the time period in which patient pain scores have consecutively decreased or remained stationary. | |
| Requirement for Rescue Analgesia | We will record whether a patient has needed rescue analgesia after randomisation and before arrival at hospital. We will also consider if any adjunctive analgesia was administered (e.g. Entonox, paracetamol, ibuprofen, or other). | |
| Proportion of patients with pain intensity score below 4/10 on NRS scale | At hospital arrival, as defined previously, the research paramedic will record a NRS pain score. We will provide the proportion, as a percentage, of each patient that achieved a score < 4/10. | If there is no hospital arrival score, we will use the last available score recorded provided it is not the baseline pain score. |
| Vital Signs | At each observation time, the respiratory rate (bpm), oxygen saturations (%), heart rate (bpm), blood pressure (mmHg) and their Glasgow Coma Scale (GCS). | |
| Glasgow Coma Scale | Three subscales measuring eyes, verbal, and motor response of each patient. The scales are as such:<br>Eyes 1-4<br>Verbal 1-5<br>Motor 1-6 | |
| Global Impression of Change | Using a 7-point Likert scale. The options offered ranging from 'very much improved' to 'very much worse' | |
| Side effects and adverse events | Measured in the following categories, 'Airway', 'Respiratory', 'Cardiovascular', 'Neurologic', and 'other'. | |
| Ambulance job cycle time | Time taken from arrival on scene to hospital arrival | |
| Number of ambulance resources | Number of doctors, paramedics, doctors, and vehicles attending scene | |

| | | |
|---|---|---|
| Cumulative IMP doses administered | Total dose of IMP administered | |
| CT scan use | If patient had a CT scan and how many | |
| Hospital or ICU admission | Yes; no option if patient is admitted to hospital or ICU | |
| Length of stay in ED, ICU, or hospital | Classed as date and time of admission to date and time of discharge | |
| **BPI-SF at 3 and 6 Months** | | |
| 9 part self-reported form which allows us to monitor the severity of the patient's pain and its effect on their daily life. Split into two sections, pain intensity and pain inference. | 9 part self-reported form which allows us to monitor the severity of the patient's pain and its effect on their daily life. | |
| Pain Severity | The pain severity part assesses the pain of the patient at its worst, least, average and now. | We can then determine the average of the 4 categories to determine pain intensity, however it is recommended that we present all 4 of the options, worst, least, average, and now. |
| Pain Interference | The interference section measures the effect of pain in 7 different tasks, walking, work, mood, enjoyment of life, relations with others, and sleep. | Measure as a mean if at least 4 of the sections have been completed. |

Descriptive statistics and results will be presented with adjusted and unadjusted models for the secondary outcomes in tables 29-43.

## 5.2 Tertiary variables and data collection

| **Variable** | **Timepoint** | **Measure** |
|---|---|---|
| Time to first noticeable pain relief | Transport to hospital | Time from initial IMP dose to participant has first noticeable pain relief |
| Time to adequate pain relief | Transport to hospital | Time from initial IMP dose to participant has adequate pain relief |
| Pain score at hospital arrival | Transport to hospital | Pain score collected at hospital arrival |
| Mechanism of injury | Transport to hospital | Blunt trauma; Penetrating trauma; Burn |

| | | |
|---|---|---|
| Injuries sustained | Transport to hospital | Facture/dislocation; Soft tissue injury; Wound/laceration |
| Body part/region injured | Transport to hospital | Head; Neck; Check & back; Abdomen; Pelvis; Upper limbs; Lower limbs |
| Analgesia post randomisation | Transport to hospital | Yes; no option with specific options offered: Entonox; Paracetamol; Ibuprofen; Other with time analgesia was given. |
| Midazolam/Naloxone administered | Transport to hospital | Yes; no option with time and dose given. |
| IMP admin | Transport to hospital | Timing and route of dose given as well as amount given in mg. |
| Discharge location | Hospital data collection | Normal residence; Rehabilitation service; Another acute hospital; Death in hospital |
| Participant entered into TARN network | Hospital data collection | Yes; no |
| Participant suffered IMP underdose | Data is collected during transport to hospital if underdose is suspected a report will be made to the clinicians within trial team to determine if underdose has occurred | Yes; no |
| Participant suffered IMP overdose | Data is collected during transport to hospital if overdose is suspected a report will be made to the clinicians within trial team to determine if overdose has occurred | Yes; no |

## 5.3 Patient Characteristics

The characteristics of enrolled patients will be summarised by treatment arm. Below is a table of the patient characteristics collected and how they are measured. Patient characteristics will be summarised in table 44, table 45, and table 46.

| Baseline characteristic | Characteristic measure |
|---|---|
| Age | Years |
| Weight | Kilograms |
| Gender, Ethnicity | Tick boxes offered (Discrete data) |
| Ambulance Service | Patients will be enrolled either by the West Midlands or Yorkshire ambulance service |
| Inclusion criteria | Inclusion criteria data will be collected and recorded by the paramedic |
| Mechanism of injury | The mechanism of injury (blunt trauma, penetrating trauma, burn), as well as the injury sustained (fracture/dislocation, soft tissue injury, wound/laceration), and body part/region of injury. |
| Vital signs | Initial participant vital signs (respiratory rate, oxygen sats, heart rate, blood pressure systolic, blood pressure diastolic, Glasgow coma scale). |

## 5.4 Analysis consideration for secondary outcomes/tertiary variables

### 5.4.1 Summary statistics

In general, continuous baseline and outcome data will be summarised with descriptive statistics, including n, mean, standard deviation, median, interquartile range and n of missing data. Categorical baseline and outcome data will be summarised with frequency counts and percentages. All the statistical analysis using statistical modelling will be presented using mean (sd) and two-sided 95% confidence intervals. In addition, some graphical presentations will be considered for some variables.

Kaplan-Meier plots will be considered for time to events, as well dose response curves and other graphical displays to identify an effective IMP dose.

### 5.4.2 Analysis strategies

***Sum of pain intensity difference (SPID)***

Sum of pain intensity difference data will be treated as continuous. Sum of pain intensity difference will be summarised and analysed using a linear regression model on the ITT. Analysis will be carried

out with and without adjustment for covariates as detailed in the primary outcome sections, with results presented in table 18 and 19.

***Total pain relief (TOTPAR)***

Total pain relief data will be treated as continuous. Total pain relief will be summarised and analysed using a linear regression model on the ITT. Analysis will be carried out with and without adjustment for covariates as detailed in the primary outcome sections, with results presented in table 29 and 30.

***Time to perceptible analgesia***

Time to perceptible analgesia will be summarised as mean, standard deviation, median, and interquartile range (IQR). We will analyse time to perceptible analgesia using time to event analysis. Analysis on the ITT population using Cox's proportional hazard model with and without adjustment for covariates as detailed in the primary outcome section, with results presented in table 29 and 30. Observations that will be censored will include those where time to perceptible analgesia has not been reached, as defined in the above table. This will include patients who withdraw or died (and have not reached perceptible analgesia) and those who at time of initial IMP administration to time of hospital arrival still have not reached perceptible analgesia.

***Time to meaningful analgesia***

Time to meaningful analgesia will be analysed in the same way as detailed for time to perceptible analgesia, with results presented in table 29 and 30. Censored observations will be similarly defined as for time to perceptible analgesia.

***Time to peak analgesia***

Time to peak analgesia will be analysed in the same way as detailed for time to perceptible analgesia, with results presented in table 29 and 30. Censored observations will be similarly defined as for time to perceptible analgesia.

***Duration of analgesia***

Duration of analgesia will be analysed in the same way as detailed for time to perceptible analgesia, with results presented in table 29 and 30. Censored observations will be similarly defined as for time to perceptible analgesia.

***Requirement for rescue analgesia***

Requirement for rescue analgesia will be treated as dichotomous. Requirement for rescue analgesia will be summarised and analysed using an ordinary logistic regression model on the ITT population. Rescue analgesia will be defined by the administration of open label ketamine or morphine before hospital arrival. We will also consider requirement for adjunctive analgesia (post randomisation entonox, paracetamol, ibuprofen). Analysis will be carried out with and without adjustment for covariates as detailed in the primary outcome section, with results presented in table 29 and 30.

***Proportion of patients with pain intensity score below 4/10 on NRS scale***

Proportion of patients with pain intensity score below 4/10 on NRS scale will be analysed in the same way as detailed for requirement for rescue analgesia, with results presented in table 29 and 30.

***Global impression of change***

Global impression of change will be treated as ordinal data. Unadjusted and adjusted analysis of the global impression of change will be summarised and analysed using a proportional odds model on the ITT population. If the assumptions for a proportional odds model do not hold, nonparametric tests will be used to compare global impression of change across treatment arms, for example the Mann-Witney U test. We will look to dichotomise the global impression of change in the case where the proportional odds for the ordinal model does not satisfy for the adjusted analysis. Adjusted analysis will use the covariates as detailed in the primary outcome section, with results presented in table 29 and 30.

***Side effects and adverse events***

Side effects and adverse events will be analysed in the same way as detailed for requirement for rescue analgesia, with results presented in table 34 and 35.

***Vital signs***

Participant vital signs and Glasgow coma scale are collected in a longitudinal data format, where observations are not collected at specific timepoints This means that vital signs observations are collected at irregular timepoints and different frequencies across participants.

Different methods have been explored to summarise and analyse these data. Observations from the same participant are not assumed to be random, therefore the randomness in the data will come from the different participants' set of observations. The most appropriate model for these data is the mixed effects model[17] without a random intercept where the residual errors correlation structure accounts for the dependency within participant observations.

An unstructured correlation structure was first explored, as this allows for the variance and covariance for each observation to be distinctly calculated, however this model specification did not converge unless some participant observations were truncated. An auto regressive structure of order 1 has therefore been adopted, as this structure assumes a lag between observations[17]. Here the observations that are closer to each other have a higher correlation than those further apart and will account for the varying timespan between observations across the participants.

Analysis will be carried out with and without adjustment for the covariates detailed in the primary outcome section, with results as presented in table 32 and 33.

***Glasgow coma scale***

Glasgow coma scale will be analysed in the same as detailed for vital signs, with results presented in table 32 and 33.

***Brief pain inventory***

The brief pain inventory score will be analysed in the same as detailed for total pain relief, with results presented in tables 40-43.

***Ambulance job cycle time***

Ambulance job cycle time will be summarised as mean, standard deviation, median, and interquartile range (IQR). We will assess the distribution of time ambulance job cycle time. If this is normally distributed, then we will use linear regression models, otherwise will be examine the difference using non-parametric statistics or gamma- distribution models on the ITT population with and without adjustment for covariates as detailed in the primary outcome section, with results presented in table 36 and 37.

***Number of ambulance clinicians in attendance***

Number of ambulance clinicians in attendance will be analysed in the same way as detailed for ambulance job cycle time, with results presented in table 36 and 37. Ambulance clinicians includes paramedics and technicians.

***Cumulative IMP doses administered***

Cumulative IMP doses administered will be analysed in the same way as detailed for ambulance job cycle time, with results presented in table 36 and 37.

***CT scan use***

CT scan use will be analysed in the same way as detailed for requirement for rescue analgesia, with results presented in table 38 and 39.

***Number of CT scans used***

Number of CT scans used will be analysed in the same way as detailed for ambulance job cycle time, with results presented in table 38 and 39.

***Hospital or ICU admission***

Hospital or ICU admission will be analysed in the same way as detailed for requirement for rescue analgesia, with results presented in table 38 and 39.

***Length of stay in ED, ICU, hospital***

Length of stay in ED, ICU, hospital will be analysed in the same way as detailed for ambulance job cycle time, with results presented in table 38 and 39.

## 5.5 Sub-groups Analysis

Subgroup analysis will be conducted for the following:

- Age (<60 and ≥60 years)
- Gender (male; female)
- Alternative parental analgesia prior to randomisation (participant received intravenous paracetamol, yes; no)

These subgroup analyses will be performed on the ITT population. The primary outcome will be used as the dependent variable and interaction with treatment. Linear regression models will be used to assess the subgroup effect, using interaction terms, subgroup by treatment, to measure the effect of each subgroup. As these analyses are post-hoc analyses which are not powered for any effect size, emphasis will not be based on the statistical testing, rather the point estimates and two-sided 95% confidence intervals, the results will be summarised in table 48.

Injury severity score, determined by the participant being entered to the TARN network was initially considered as a subgroup analysis. However, there would be insufficient data to complete the subgroup analysis.

## 5.6 Secondary analysis

In addition to the standard frequentist analysis that was originally planned at the start of the trial, we will also perform a Bayesian analysis, to aid the interpretation of the results. If the assumptions used in the trial design are found to be incorrect, for example the observed standard deviation of the primary outcome is higher than expected, the accuracy of the trial results may be reduced, which would lower the chance of a treatment effect reaching the threshold for statistical significance. In this situation, interpretation of the results by clinicians and other decision makers will be helped by producing a quantitative summary of the probability that ketamine is a superior analgesia than morphine for acute pain, considering existing evidence and the trial's results through Bayesian analysis.

The analysis will model the primary outcome, SPID, using Bayesian linear regression models, and including the same covariates as the main analysis. The means of the posterior distribution for each of the covariates and treatment group will be calculated from this model. Sensitivity analysis will determine the effects of the prior, this is expected to be small due to the large amount of data available from the trial.

# Section 6: Introduction to Health Economic Analysis

## 6.1 Purpose of the health economic analysis plan

The objective of the health economics analysis is to inform decision makers regarding the cost-effectiveness of paramedic administered ketamine compared to morphine for the management of acute severe pain from traumatic injury. The purpose of the health economics analysis plan (HEAP) is to outline the framework of methods that will be used to analyse the health economic components of the trial to ensure the integrity of the cost-effectiveness analysis.

## 6.2 Type of economic evaluation

As recommended, the primary health economic analysis will be a cost-utility analysis with incremental quality adjusted life years (QALYs) as the primary health economic outcome[1]. Following NICE guidance, the EQ-5D-5L will be used for the construction of QALYs (see section 7.1.1)[1].

## 6.3 Perspective

A healthcare and personal social services (PSS) will be adopted in the primary analysis as recommended by NICE[1].

## 6.4 Time Horizon

The primary health economic analysis will run concurrently to the effectiveness analysis. The EQ-5D-5L will be collected at three and six-months post-randomisation. The time horizon will therefore be the 6-month period post-randomisation. Should outcomes not have converged after 6 months, we will consider the development of a decision analytic model to extrapolate the cost-effectiveness results over a lifetime horizon (see section 8.5).

## 6.5 Discounting

Given the trial-based analysis has a time-horizon of 6 months, costs and QALYs will not be discounted. Should longer-term decision modelling be conducted, we will use the 3.5% annual discount rate as recommended by NICE to discount future costs and QALYs[1].

## 6.6 Intention to treat

The health economic analysis will adopt the principle of 'intention to treat'[18]. This means that the health economic analysis will analyse individuals according to the trial arms to which they were randomised.

## 6.7 Missing data

Missing data is a common occurrence within randomised clinical trials and needs to be considered within the health economic analysis[19]. Missing data will be explored, and if non-trivial (5% or more in either costs or QALYs)[20], the base case analysis will use multiple imputation (MI)[21] as the preferred method for estimating results in the presence of missing data. MI uses the observed data and samples from the predictive distribution to create multiple datasets[22]. Under the assumption of missing at random, this provides unbiased estimates; this allows uncertainty surrounding estimates to be maintained whilst allowing full use of the available data (see section 8.2).

# Section 7: Health Economic Outcomes

## 7.1 Primary health economic outcome

As recommended by NICE, incremental quality adjusted life years (QALYs) will be used as the primary measure of health consequence for the health economic analysis[1].

### 7.1.1 Quality adjusted life years (QALYs)

#### *Estimating QALYs*

QALYs combine both mortality and morbidity into a single measure that can be compared across contexts within the healthcare service. To calculate QALYs it is necessary to combine a preference-based health-related quality of life outcomes with survival benefits. In this study, we are using the EQ-5D-5L[23] at two time points (3 months, 6 months). The EQ-5D-5L is a preference-based measure of health-related quality of life and is recommended by NICE for use in economic evaluation[1]. The measure contains a descriptive system with five dimensions of health, each containing five levels. There exist value-sets[24,25] that allow the calculation of *utility* scores for any given set of responses to the EQ-5D-5L descriptive system. A utility score is a score on a cardinal scale indexed at zero and one, where zero represents death, and one represents full health (negative states are possible). These utility values can be combined with survival benefits to derive QALYs. Although a new UK specific EQ-5D-5L value set exists[24], it has been a subject of controversy[26]. Currently NICE instead recommends[27] the use of the Van Hout et al[25] 'cross-walk' algorithm.

A challenge to the analysis is the lack of baseline EQ-5D-5L measurement which is required for the calculation of QALYs for the duration of follow-up from randomisation. For ethical, logistical and pragmatic reasons, it is not possible to capture baseline EQ-5D-5L measurements in patients suffering acute pain following trauma within this trial. This is not uncommon within trials involving emergency and critical care settings[28]. Ideally, the EQ-5D-5L would be completed at the time of randomisation or as soon as possible afterwards. This however is not possible in this trial. A systematic review of emergency and critical care studies[28] identified four strategies that have been used in such situations. First, the most common approach (57% of all studies identified by the systematic review) is to assign a fixed health utility to all participants at baseline. Second, some studies (29%) estimated QALYs using only the available data and implicitly ignored any benefits that occurred before the first follow up data collection point. One study (7%) asked patients to retrospectively recall their health state at randomisation. Finally, one study (7%) mapped health states onto EQ-5D-3L using expert evidence to derive baseline health states. The primary analysis will use a fixed baseline approach for all participants. This fixed value will be derived by mapping the 'typical' acute pain trauma case to the EQ-5D-5L using expert opinion. The sensitivity of this assumption will be tested within sensitivity analyses (see 8.4.2). Sensitivity analyses will include assigning different values to patients according to severity as determined by registration to the Trauma Audit and Research Network (TARN). TARN can be used as proxy for severity as the most serious trauma patients will be registered onto TARN whilst less severe cases will not (non-TARN). We will then use expert opinion to estimate a baseline EQ-5D profile for both TARN and non-TARN patients.

QALYs for each patient will be calculated by using the utility values at baseline, 3 months and 6 months. QALYs will be calculated by linearly interpolating utility values at the three time points and

calculating the area under the curve using the trapezium rule[29]. QALYs will be calculated for each patient in the trial.

## 7.2 Resource Use and Costing

To calculate costs for use in cost-utility analysis it is necessary to capture information on resources used for both the control and intervention arm. Costs within this trial can be split into the following broad components:

- Direct intervention costs (medication costs)
- Direct healthcare and PSS costs (e.g. medication for side-effects, outpatient appointments, community care)
- Other societal costs (e.g. value of lost productivity, out of pocket expenses)

NICE's guide to methods of technology appraisal recommend costing from an NHS and personal social services (PSS) perspective[1]. The primary analysis will only consider the first two categories of costs; broader societal costs will be included within a sensitivity analysis. To calculate costs, it is first necessary to capture resource use, and then apply unit costs to each resource input. The price year for the analysis will be informed by the latest available base year for common costing resources at time of analysis.

### 7.2.1 Direct intervention resource use and costs

The PACKMaN trial focuses on administration of two alternative medications for pain relief in patients with severe pain. The intervention arm will receive ketamine hydrochloride whilst the control arm will receive morphine sulphate. The intervention components and associated resource use are summarised within the table below. This table shows what the components are, how they will be collected and where unit cost sources may be sourced from.

*Direct intervention resource use and cost sources*

| ***Intervention arm*** | | | |
|---|---|---|---|
| **Resource type** | **Resource use** | **How collected** | **Unit costs source** |
| Ketamine hydrochloride | Number and ml of doses administered. | Recorded within ambulance service data | NHSBSA[29] |
| ***Control arm*** | | | |
| Morphine sulphate | Number and ml of doses administered. | Recorded within ambulance service data | NHSBSA[29] |

### 7.2.2 Healthcare and social care resource use

In according with NICE guidance, we will capture healthcare and PSS costs for both arms of the trial[1]. This will include, within-ambulance costs, inpatient care, outpatient care, community care, accident and emergency admission, medication, and personal social services. The methods for capturing the resource use and the sources for unit costs are outlined in the table below. Within ambulance costs will be captured through the ambulance service data form, index admission costs will be collected

via the hospital data collection form, whilst the remaining costs will be collected through the case report forms at 3 and 6 months.

*Health and social care costs for both arms*

| Resource type | Resource use | How collected | Unit cost sources |
|---|---|---|---|
| Within ambulance – rescue analgesia medication | Entonox, paracetamol, ibuprofen, other painkiller | Ambulance service data form | NHSBSA[30] |
| Within ambulance – side-effects medication | Midazolam or naloxone | Ambulance service data form | NHSBSA[30] |
| Inpatient care – index admission | Length of stay and number of days at each level of care | Hospital data collection form | NHS Reference Costs[31] |
| Index admission | CT scans | Hospital data collection form | NHS Reference Costs[31] |
| Inpatient care – follow up | Specified within CRFs | CRFs at 3m and 6m | NHS Reference Costs[31] and PSSRU[32]. HRG4+ 'Code to Group'[33] used to allocate inpatient care to HRG groups for costing. |
| Outpatient care | Specified within CRFs | CRFs at 3m and 6m | NHS Reference Costs[31] and PSSRU[32]. |
| Community care | Specified within CRFs | CRFs at 3m and 6m | NHS Reference Costs[31] and PSSRU[32]. |
| Medication | Specified within CRFs | CRFs at 3m and 6m | NHSBSA[30] |
| Personal social services | Specified within CRFs | CRFs at 3m and 6m | PSSRU[32] unit costs |

### 7.2.3 Wider costs

Within an additional sensitivity analysis, we will also be collecting information related to days lost from work and out of pocket expenses.

*Wider costs*

| Resource type | Resource use | How collected | Unit cost sources |
|---|---|---|---|
| Absence from work and out of pocket expenses | Specified within CRFs | CRFs at 3m and 6m | Stated in CRFs |

# Section 8: Health Economic Analysis

## 8.1 Descriptive analysis

Resource use, costs and EQ-5D utility scores will first be presented descriptively to inform parameters for future health economic studies (this includes means and standard deviations). Costs will be calculated for all perspectives outlined previously.

## 8.2 Addressing missing data with multiple imputation

If the proportion of missing data for either costs or QALYs is more than 5% we will use multiple imputation to impute data within the base-case analysis. This data will then be used in the incremental analysis of costs, QALYs and the joint cost-effectiveness analysis. A complete case analysis will be included as a sensitivity analysis. Stata[34] will be used to conduct both the multiple imputation and the analysis of imputed data. The 'mi impute chained' command which uses chained equations to generate imputed datasets will be used for each treatment group. Within the imputation regression framework, we will include both costs and EQ-5D-5L at each timepoint as both imputed and predictor variables. We will also include any auxiliary variables that are found to be highly correlated ($r>0.4$)[35] with costs or EQ-5D-5L, or are believed to be associated with missingness. We will use predictive mean matching drawing from the 5 nearest 'neighbours', this is important for the avoidance of drawing implausible values, e.g., utility values over 1, and 'negative costs'. The number of iterations will be guided by the fraction of missing information[20]. We will then use the 'mi estimate' functionality within Stata to run the analyses (specified in subsequent sections) within each dataset and to combine results using Rubin's combination rule to allow inferential statistics. Imputations will be added until estimates stabilise. We will examine the validity of the imputed data by comparing the distribution of the imputations and observed data both visually and statistically.

## 8.3 Single end point analysis: incremental costs and incremental QALYs

Before conducting the joint cost-effectiveness analysis, we will examine the impact of the intervention on incremental costs and incremental QALYs in isolation. Differences between the two arms will be assessed using a regression framework. The exact specification will depend upon the nature of the data. Costs will be estimated by combining resource use data with unit costs. Costs for each patient within the trial will be calculated and incremental costs between the two arms will be estimated. Again, a regression framework will be used, and its exact specification will be informed by the nature and distribution of the data.

## 8.4 Cost-effectiveness analysis and characterising uncertainty

We will use bivariate regression analysis in the form of seemingly unrelated regressions (with bootstrapping) for the joint analysis of costs and QALYs. This framework offers several benefits: first of all it accounts for the existence of correlation between costs and outcomes for patients; second it allows the inclusion of covariates within the analysis, this is particularly relevant for the adjustment of baseline utility with respect to QALYs accrued; third it is generally robust to non-normal distributions; fourth, it can account for clustering either by including clusters as a fixed effect or by running the seemingly unrelated regressions in a multi-level framework. Non-parametric bootstrapping will be used to examine the level of uncertainty by presenting the bootstrapped results on a cost-effectiveness plane, and by generating cost-effectiveness acceptability curves (CEACs). Should there be distributional or computational concerns (e.g. difficulty in fitting a multi-

level seemingly unrelated regression model with imputed data in Stata) then we may consider combining costs and outcomes within a univariate net-benefit regression framework.

### 8.4.1 Characterizing uncertainty for decision makers

Cost-effectiveness acceptability curves (CEACs) will be used to characterise uncertainty. CEACs show the probability that the intervention is cost-effective compared to the control at different levels of willingness to pay for QALYs and explicitly highlight the uncertainty within the decision problem. To avoid the issues related to uncertainty around cost-effectiveness ratios we will calculate net-monetary benefit for each of the bootstrapped iterations:

$$\Delta NB = \Delta e\gamma - \Delta c$$

In this instance, $\Delta NB$ refers to the incremental net monetary benefit, $\Delta e$ reflects the incremental outcome of interest, incremental QALYs, whilst $\Delta c$ refers to the incremental costs. The symbol $\gamma$ refers to the decision maker's willingness to pay per QALY. For each of the bootstrapped cost-effectiveness samples we will calculate the associated net-monetary benefit across a range of levels of willingness to pay ($\gamma$). For each $\gamma$ the proportion of iterations where net-benefit is greater than zero can be used estimate the probability that the intervention is more cost-effective at that willingness to pay. This will be conducted for a range of $\gamma$ including £20,000 and £30,000 per QALY as specified by NICE and plotted to derive a CEAC[1].

### 8.4.2. Sensitivity analyses

In addition to the probabilistic sensitivity analysis outlined above we will also consider sensitivity analyses, these will include:

- Costing from a societal perspective
- Complete case analysis (assuming missing data exceeds 5%)
- Changing baseline utility assumptions
- Subgroup analyses as specified within the statistical analysis plan
- Cost per sum of pain intensity difference (SPID) score point reduction

## 8.5 Decision modelling

The primary trial-based analysis will focus on the costs and QALYs accrued during the trial period. There however is potential for costs and benefits to accrue beyond the trial period. If outcomes have not converged by the 6m timepoint we will consider extrapolating the results over a longer time horizon using a decision analytic model. This would involve combining the trial data with external sources to estimate the long-term cost-effectiveness of the intervention. Any costs and benefits accruing after the first year would be discounted at a rate of 3.5% per year and full probabilistic sensitivity analysis would be conducted in line with the NICE reference case[1]. A decision as to the necessity of building a decision analytic model and its specification will be made following discussion between the health economists and the trial team following preliminary analysis of the data. This will be informed by considerations such as the conclusiveness and direction of within trial results. For example, if the control dominates the intervention and extrapolation would only increase the strength of this result then there is little need to extrapolate further as the intervention should be rejected.

## 8.6 Value of information analysis

Should a decision model be developed we will also conduct a value of information (VoI) analysis to examine the expected value of future research. The VoI analysis will entail the calculation of the expected value of perfect information (EVPI) using data from the cost-effectiveness analysis. EVPI can be conceptualised as the expected gain from eliminating uncertainty within the decision problem, or put another way, the expected loss associated with uncertainty. This is essentially the probability of the decision being wrong multiplied by the average consequence of being wrong[36]. This allows us to calculate the estimated value of 'perfect knowledge' which is the maximum value society should be willing to pay for additional evidence to reduce uncertainty around whether the intervention or the control is more cost-effective[37]. Using the trial data, we will calculate the per person EVPI using a willingness to pay threshold of £30,000 per QALY, this representing the threshold NICE uses in practice[38]. This will be multiplied by the number of potential beneficiaries of the intervention within the NHS along with the technological horizon (years) to estimate population EVPI. Discounting of EVPI will be applied at 3.5% beyond the first year.

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Figure 1: CONSORT diagram

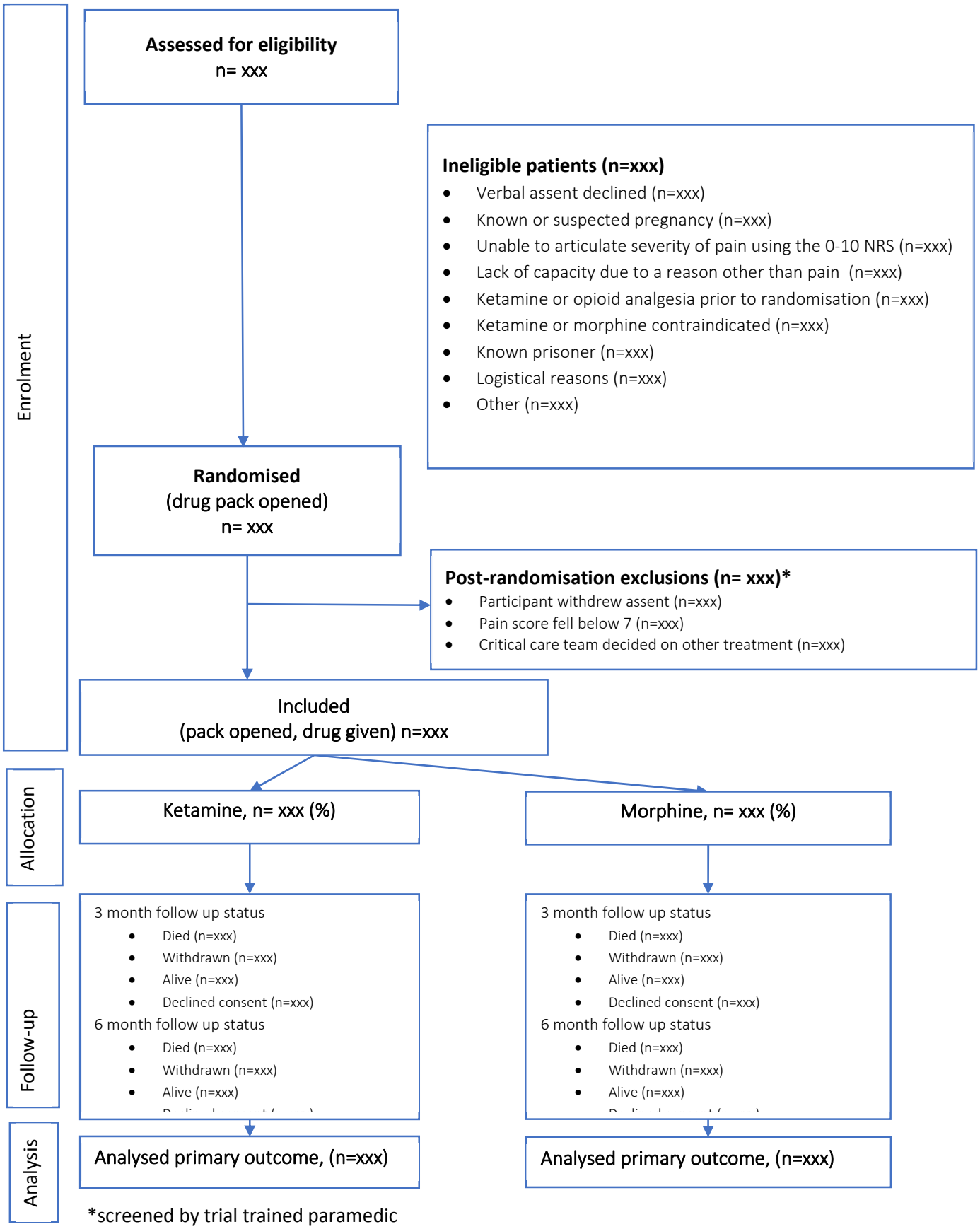

**Figure 2: Patient flow of PACKMaN trial from recruitment to hospital discharge**

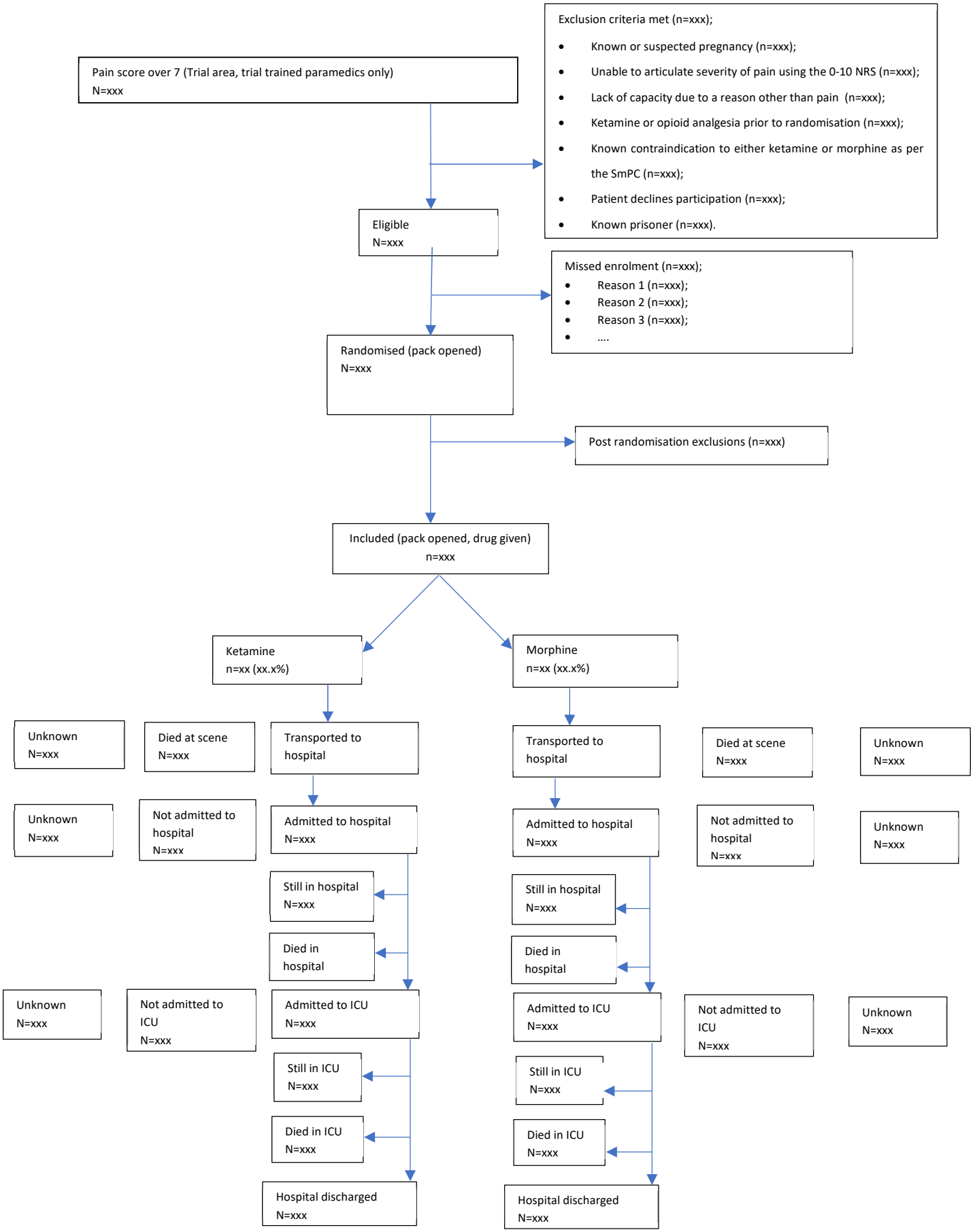

**Table 1: Randomised patients by treatment and ambulance service – assessment of balance of randomisation**

| | Ketamine | Morphine | Total |
|---|---|---|---|
| Ambulance service 1 | N(%) | N(%) | N |
| Ambulance service 2 | N(%) | N(%) | N |
| TOTAL | N(%) | N(%) | N |

Percentages are based within each treatment arm

**Table 2: Current recruitment by treatment and ambulance service**

| | Number of months recruitment | Average number of patients recruited per month | Ketamine | Morphine | Total |
|---|---|---|---|---|---|
| SITE | N | N | N(%) | N(%) | N |
| Ambulance service 1 | N | N | N(%) | N(%) | N |
| Ambulance service 2 | N | N | N(%) | N(%) | N |
| TOTAL | N | N | N | N | N |

Percentages are based within each treatment arm

**Table 3: Reasons for missed enrolment, per ambulance service and total**

| Missed enrolment reasons | Ambulance service 1 | Ambulance service 2 | Total |
|---|---|---|---|
| Total | | | |
| Paramedic trained but not carrying pack | N(%) | N(%) | N(%) |
| Paramedic trained but pack used previously on shift | N(%) | N(%) | N(%) |
| Other reason | N(%) | N(%) | N(%) |

Percentages are based within each ambulance service

**Table 4a: Reasons for ineligibility, per ambulance service and total**

| Eligibility Criteria | Ambulance service 1 | Ambulance service 2 | Total |
|---|---|---|---|
| Total | | | |
| Under 16 years of age | N(%) | N(%) | N(%) |
| Patient reported pain score is below 7 | N(%) | N(%) | N(%) |
| Intravenous and intraosseous access not obtained | N(%) | N(%) | N(%) |
| Paramedic determined patient did not require IV morphine or equivalent | N(%) | N(%) | N(%) |
| Known or suspected pregnancy | N(%) | N(%) | N(%) |
| Unable to articulate pain severity | N(%) | N(%) | N(%) |
| Lack of capacity due to reason other than pain | N(%) | N(%) | N(%) |
| Ketamine or opioid analgesia prior to randomisation | N(%) | N(%) | N(%) |
| Known contraindication to either ketamine or morphine, per SmPC | N(%) | N(%) | N(%) |

| | | | |
|---|---|---|---|
| Patient declined participation | N(%) | N(%) | N(%) |
| Known prisoner | N(%) | N(%) | N(%) |
| Other | N(%) | N(%) | N(%) |

Percentages are based within each ambulance service

**Table 4b: Post randomisation exclusion reasons**

| TNO | Date of randomisation | Reason for no primary outcome data |
|---|---|---|
| | | |

**Table 5: Participant trial flow of all randomised participants by treatment arm**

| Time period | Patient flow | Ketamine | Morphine | Total |
|---|---|---|---|---|
| At randomisation | TOTAL participants RANDOMISED | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| From randomisation to arrival in hospital | Alive with data collection | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Deaths | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Withdrawals from trial treatment (but continued trial participations) | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Withdrawal from study (after consent) | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Did not consent | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Lost to follow-up | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| From arrival in hospital to discharge | Alive with data collection | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Deaths | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Withdrawal from study (after consent) | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Did not consent | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Lost to follow-up | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| From discharge to 3-month follow-up | Alive with data collection | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Deaths | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Withdrawal from study (after consent) | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Did not consent | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Lost to follow-up | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Alive with data collection | Xxx (xx.x%) | Xxx (xx.x%) | xxx |

| | | | | |
|---|---|---|---|---|
| From discharge to 6-month follow-up | Deaths | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Withdrawal from study (after consent) | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Did not consent | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| | Lost to follow-up | Xxx (xx.x%) | Xxx (xx.x%) | xxx |

Percentages are based within each column

**Table 6: Withdrawals by treatment arm**

| Time period | Type of Withdrawals | Ketamine | Morphine | Total |
|---|---|---|---|---|
| Randomisation to hospital arrival | Withdrawn from treatment | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| Randomisation to hospital arrival | Withdrawn from study | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| Randomisation to discharge | Withdrawn from study | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| Randomisation to 3 months | Withdrawn from study | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| Randomisation to 6 months | Withdrawn from study | Xxx (xx.x%) | Xxx (xx.x%) | xxx |
| Total | | Xxx | Xxx | xxx |

Percentages are based within each column

**Listing 1 reasons for withdrawal**

**Table 7: Deaths by treatment arm**

| Time period | Ketamine | Morphine | Total |
|---|---|---|---|
| Randomisation to hospital arrival | N(%) | N(%) | N |
| Randomisation to hospital arrival | N(%) | N(%) | N |
| Randomisation to discharge | N(%) | N(%) | N |
| Randomisation to 3 months | N(%) | N(%) | N |
| Randomisation to 6 months | N(%) | N(%) | N |
| Total | N | N | N |

Percentages are based within each column

**Table 8a: Summary of Protocol violations by treatment arm**

| PROTOCOL VIOLATIONS | Ketamine | Morphine | Total |
|---|---|---|---|
| No of patients with at least one protocol violations | N(%) | N(%) | N |
| Number of protocol violations | N(%) | N(%) | N |
| TOTAL | N | N | N |

Percentages are based within each column

**Table 8b: Details of Protocol violations by treatment arm**

Ketamine

| CAPA Number | TNO | Issue | Date aware | Date resolved/actions implemented | File note/ deviation/ violation/ breach |
|---|---|---|---|---|---|
| | XX | | | | |
| | XX | | | | |

Morphine

| CAPA Number | TNO | Issue | Date aware | Date resolved/actions implemented | File note/ deviation/ violation/ breach |
|---|---|---|---|---|---|
| | XX | | | | |
| | XX | | | | |

**Table 9a: Summary of Protocol deviations by treatment arm**

| PROTOCOL DEVIATIONS | Ketamine | Morphine | Total |
|---|---|---|---|
| No of patients with at least one protocol violations | N(%) | N(%) | N |
| Number of protocol violations | N(%) | N(%) | N |
| TOTAL | N | N | N |

Percentages are based within each column

**Table 9b: Details of Protocol deviations by treatment arm**

Ketamine

| CAPA Number | TNO | Issue | Date aware | Date resolved/actions implemented | File note/ deviation/ violation/ breach |
|---|---|---|---|---|---|
| | XX | | | | |
| | XX | | | | |

Morphine

| CAPA Number | TNO | Issue | Date aware | Date resolved/actions implemented | File note/ deviation/ violation/ breach |
|---|---|---|---|---|---|
| | XX | | | | |
| | XX | | | | |

**Table 10: Number of Serious adverse events**

| SERIOUS ADVERSE EVENTS | Ketamine | Morphine | Unadjusted estimate (95% CI); p-value | Total |
|---|---|---|---|---|
| No of patients with at least one SAE | N(%) | N(%) | | N |
| Number of SAE | N(%) | N(%) | | N |
| TOTAL | N | N | | N |

Percentages are based within each column

LISTING 2: Serious adverse events by treatment arm

**Table 11: Number of Adverse events**

| ADVERSE EVENTS | Ketamine | Morphine | Unadjusted estimate (95% CI); p-value | Total |
|---|---|---|---|---|
| No of patients with at least one AE | N(%) | N(%) | | N |
| Number of AE | N(%) | N(%) | | N |
| TOTAL | N | N | | N |

Percentages are based within each column

LISTING 3: Adverse events by treatment arm

**Table 12: Unblinding requests by treatment arm**

| | Ketamine | Morphine | Total |
|---|---|---|---|
| Total number of unblinding requests | Xxx (xx.x%) | Xxx (xx.x%) | xxx |

**Table 13: Participants recruited, and paramedics trained by paramedic experience level**

Intervention: Ketamine

| | Recruited | % Recruited | Trial-trained | % Trial-trained |
|---|---|---|---|---|
| Band 6 | xxx | xx.x% | xxx | xx.x% |
| NQPs | xxx | xx.x% | xxx | xx.x% |
| No longer in service | xxx | xx.x% | xxx | xx.x% |
| Total | xxx | xx.x% | xxx | xx.x% |
| | | | | |
| WMAS Band 6 | xxx | xx.x% | xxx | xx.x% |
| WMAS NQPs | xxx | xx.x% | xxx | xx.x% |
| WMAS No longer in service | xxx | xx.x% | xxx | xx.x% |
| WMAS Total | xxx | xx.x% | xxx | xx.x% |
| | | | | |

| | | | | |
|---|---|---|---|---|
| YAS band 6 | xxx | xx.x% | xxx | xx.x% |
| YAS NQPs | xxx | xx.x% | xxx | xx.x% |
| YAS UK - no longer in service | xxx | xx.x% | xxx | xx.x% |
| YAS Total | xxx | xx.x% | xxx | xx.x% |

Percentages are based within each column

Intervention: Morphine

| | Recruited | % Recruited | Trial-trained | % Trial-trained |
|---|---|---|---|---|
| Band 6 | xxx | xx.x% | xxx | xx.x% |
| NQPs | xxx | xx.x% | xxx | xx.x% |
| No longer in service | xxx | xx.x% | xxx | xx.x% |
| Total | xxx | xx.x% | xxx | xx.x% |
| | | | | |
| WMAS Band 6 | xxx | xx.x% | xxx | xx.x% |
| WMAS NQPs | xxx | xx.x% | xxx | xx.x% |
| WMAS No longer in service | xxx | xx.x% | xxx | xx.x% |
| WMAS Total | xxx | xx.x% | xxx | xx.x% |
| | | | | |
| YAS band 6 | xxx | xx.x% | xxx | xx.x% |
| YAS NQPs | xxx | xx.x% | xxx | xx.x% |
| YAS UK - no longer in service | xxx | xx.x% | xxx | xx.x% |
| YAS Total | xxx | xx.x% | xxx | xx.x% |

Percentages are based within each column

**Table 14: Serious adverse events, adverse events and non-compliance frequencies for paramedic experience level**

Intervention: Ketamine

| | Band 6 | NQP | Unadjusted estimate (95% CI); p-value |
|---|---|---|---|
| Serious Adverse Events | Xxx (xx.x%) | Xxx (xx.x%) | |
| Adverse Events | Xxx (xx.x%) | Xxx (xx.x%) | |
| Non-compliances | Xxx (xx.x%) | Xxx (xx.x%) | |

Percentages are based within each column

**Table 15: Non compliances details for paramedic experience level**

Intervention: Ketamine

| TNO | Site | NC | NC details | NC classification | Paramedic experience level (e.g. NQP1, NQP2?) | Any notes |
|---|---|---|---|---|---|---|
| …<br>… | | | | | | |

Intervention: Morphine

| TNO | Site | NC | NC details | NC classification | Paramedic experience level (e.g. NQP1, NQP2?) | Any notes |
|---|---|---|---|---|---|---|
| …<br>… | | | | | | |

**Table 16: Serious adverse events details for paramedic experience level**

Intervention: Ketamine

| TNO | Site | SAE | Causality | SAE resolved? | Paramedic experience level (e.g. NQP1, NQP2?) | Any notes |
|---|---|---|---|---|---|---|
| | | | | | | |

Intervention: Morphine

| TNO | Site | SAE | Causality | SAE resolved? | Paramedic experience level (e.g. NQP1, NQP2?) | Any notes |
|---|---|---|---|---|---|---|
| | | | | | | |

**Table 17: Adequacy of blinding**

| Paramedic guess | Ketamine | Morphine | Total | P value |
|---|---|---|---|---|
| Correct | Xx (xx.x%) | Xx (xx.x%) | Xx | |
| Incorrect | Xx (xx.x%) | Xx (xx.x%) | xx | 0.xx |

Percentages are based within each column

**Table 18: Primary outcome summary statistics of all randomised participants by treatment arm**

| | | Ketamine | Morphine | Total |
|---|---|---|---|---|
| Initial pain score at eligibility | Mean(sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Sum of pain intensity (SPID) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |

Percentages are based within each column

**Table 19: Primary outcome study outcome at baseline, [mean(sd)]**

| | Ketamine | Morphine | Unadjusted estimate (95% CI); p-value | Adjusted estimate (95% CI)*; p-value |
|---|---|---|---|---|
| Sum of pain intensity (SPID) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x); 0.xx |

Percentages are based within each column

**Table 20: Baseline demographic characteristics of randomised participants summarised by compliance status (compliers and non-compliers)**

| Baseline demographics | | Complier | Non-complier | Unadjusted estimate (95% CI); p-value |
|---|---|---|---|---|
| Age | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | |
| Gender | Male | N (xx%) | N (xx%) | |
| | Female | N (xx%) | N (xx%) | |
| | Transgender | N (xx%) | N (xx%) | |
| | Other | N (xx%) | N (xx%) | |
| | Not disclosed | N (xx%) | N (xx%) | |
| | Missing | N (xx%) | N (xx%) | |
| Ethnicity | White | N (xx%) | N (xx%) | |
| | Black | N (xx%) | N (xx%) | |
| | Mixed | N (xx%) | N (xx%) | |
| | Any other ethnic group | N (xx%) | N (xx%) | |
| | Asian | N (xx%) | N (xx%) | |
| | Ethnicity not given | N (xx%) | N (xx%) | |
| | Missing | N (xx%) | N (xx%) | |
| Weight | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | |

Percentages are based within each column

**Table 21: Primary outcome and mortality summary statistics of randomised participants summarised by compliance status (compliers and non-compliers), [mean (sd)]**

| | Complier | Non-complier | Unadjusted estimate (95% CI); p-value |
|---|---|---|---|
| Sum of pain intensity (SPID) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Mortality | N (xx%) | N (xx%) | |

Percentages are based within each column

**Table 22: Injury characteristics of randomised participants summarised by compliance status (compliers and non-compliers)**

| | | | Complier | Non-complier | Unadjusted estimate (95% CI); p-value |
|---|---|---|---|---|---|
| Mechanism of Injury: | Blunt Trauma | | N (xx%) | N (xx%) | |
| | Penetrating Trauma | | N (xx%) | N (xx%) | |
| | Burn | | N (xx%) | N (xx%) | |
| | Missing | | N (xx%) | N (xx%) | |
| Injuries sustained: | Fracture/ dislocation | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Soft tissue injury | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Wound/ laceration | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| Body part/region injured: | Head | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Neck | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Chest & back | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Abdomen | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Pelvis | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Upper limbs | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Lower limbs | Yes | N (xx%) | N (xx%) | |

| | | | | | |
|---|---|---|---|---|---|
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |

Percentages are based within each column

**Table 23: Secondary outcomes summary statistics of randomised participants summarised by compliance status (compliers and non-compliers)**

| | Complier | Non-complier | Unadjusted estimate (95% CI); p-value |
|---|---|---|---|
| Total pain relief (TOTPAR), mean(sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Time to perceptible analgesia, median (IQR) | (n=xxx)<br>xx.x (xx.x to xx.x) | (n=xxx)<br>xx.x (xx.x to xx.x) | |
| Time to meaningful analgesia, median (IQR) | (n=xxx)<br>xx.x (xx.x to xx.x) | (n=xxx)<br>xx.x (xx.x to xx.x) | |
| Time to peak analgesia, median (IQR) | (n=xxx)<br>xx.x (xx.x to xx.x) | (n=xxx)<br>xx.x (xx.x to xx.x) | |
| Duration of analgesia, median (IQR) | (n=xxx)<br>xx.x (xx.x to xx.x) | (n=xxx)<br>xx.x (xx.x to xx.x) | |
| Patient global impression of change, N (%) | | | |
| Very much improved | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| Much improved | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| Minimally improved | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| No change | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| Minimally worse | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| Much worse | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| Very much worse | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| Required rescue analgesia, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |

| | | | |
|---|---|---|---|
| Final pain score below 4/10, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |

Percentages are based within each column

**Table 24: Ambulance vital signs characteristics of randomised participants summarised by compliance status (compliers and non-compliers)**

| | Complier | Non-complier | Unadjusted estimate (95% CI); p-value |
|---|---|---|---|
| Blood pressure Systolic (mmHg) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Blood pressure Diastolic (mmHg) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Pulse rate (bpm) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Respiration rate (bpm) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Oxygen sats (%) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Glasgow coma scale (GCS) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |

**Table 25: Expected adverse event of randomised participants summarised by compliance status (compliers and non-compliers)**

| | | | Complier | Non-complier | Unadjusted estimate (95% CI); p-value |
|---|---|---|---|---|---|
| Experienced adverse event | | | N (xx%) | N (xx%) | |
| Airway | Vomiting | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Aspiration | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Advanced airway management | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| Respiratory | Desaturation | Yes | N (xx%) | N (xx%) | |

| | | | | | |
|---|---|---|---|---|---|
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Need for ventilatory support | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| Cardiovascular | Arrhythmia | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Hypotension | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Hypertension | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| Neurologic | Sedation | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Excitatory movements | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Adverse behavioural reactions | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| Other | Allergic reaction | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |
| | Nausea | Yes | N (xx%) | N (xx%) | |
| | | No | N (xx%) | N (xx%) | |
| | | Missing | N (xx%) | N (xx%) | |

Percentages are based within each column

**Table 26: Ambulance resource use of randomised participants summarised by compliance status (compliers and non-compliers)**

| | Complier | Non-complier | Unadjusted estimate (95% CI); p-value |
|---|---|---|---|
| Ambulance job cycle time, median (IQR) | (n=xxx)<br>xx.x (xx.x to xx.x) | (n=xxx)<br>xx.x (xx.x to xx.x) | |
| Cumulative IMP dose, mean(sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Number of ambulance clinicans, mean(sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Number of paramedics, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |

| | | | |
|---|---|---|---|
| Number of ambulance technicians/students, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Number of doctors , mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Number of others attending, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |

Percentages are based within each column

**Table 27: Hospital stay and procedures of randomised participants summarised by compliance status (compliers and non-compliers)**

| | Complier | Non-complier | Unadjusted estimate (95% CI); p-value |
|---|---|---|---|
| Length of stay in ED, median (IQR) | (n=xxx)<br>xx.x (xx.x to xx.x) | (n=xxx)<br>xx.x (xx.x to xx.x) | |
| Patient admitted to hospital, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| Admitted to critical care, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| Days in receiving level 1/2 critical care, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Days in receiving level 3 critical care, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Days in receiving unknown level of critical care, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Length of stay hospital, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Participant entered to TARN, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| CT Scan use, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | |
| Number of CT scans per patient, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |

Percentages are based within each column

**Table 28: Long term outcomes of randomised participants summarised by compliance status (compliers and non-compliers)**

| | | Complier | Non-complier | Unadjusted estimate (95% CI); p-value |
|---|---|---|---|---|
| Pain severity | Overall | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| | Worst pain | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| | Least pain | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| | Average pain | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| | Pain now | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |
| Pain interference | | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | |

Percentages are based within each column

**Table 29: Secondary outcomes and tertiary variables summary statistics of all randomised participants by treatment arm**

| | | Ketamine | Morphine | Total |
|---|---|---|---|---|
| Total pain relief (TOTPAR) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Time to perceptible analgesia | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Time to meaningful analgesia | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Time to peak analgesia | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Duration of analgesia | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Time to first noticeable pain relief (mins)* | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Time to first adequate pain relief (mins)* | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |

| | | | | |
|---|---|---|---|---|
| Time taken to arrive to hospital* | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Patient global impression of change | Very much improved | N (xx%) | N (xx%) | N (xx%) |
| | Much improved | N (xx%) | N (xx%) | N (xx%) |
| | Minimally improved | N (xx%) | N (xx%) | N (xx%) |
| | No change | N (xx%) | N (xx%) | N (xx%) |
| | Minimally worse | N (xx%) | N (xx%) | N (xx%) |
| | Much worse | N (xx%) | N (xx%) | N (xx%) |
| | Very much worse | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |

*time taken from point of randomisation

Percentages are based within each column

**Table 30: Secondary outcome study outcome at baseline**

| | Ketamine | Morphine | Unadjusted estimate (95% CI); p-value | Adjusted estimate (95% CI)*; p-value | Unadjusted Difference (95% CI) | Adjusted Difference (95% CI) |
|---|---|---|---|---|---|---|
| Total pain relief (TOTPAR), mean(sd) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x) ; 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx | N/a | N/a |
| Time to perceptible analgesia, median (IQR) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MDND, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx | | |
| Time to meaningful analgesia, median (IQR) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | HR, x.xx (x.xx to x.xx) ; 0.xx | HR, x.xx (x.xx to x.xx) ; 0.xx | | |
| Time to peak analgesia, median (IQR) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | HR, x.xx (x.xx to x.xx) ; 0.xx | HR, x.xx (x.xx to x.xx) ; 0.xx | | |
| Duration of analgesia, median (IQR) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | HR, x.xx (x.xx to x.xx) ; 0.xx | HR, x.xx (x.xx to x.xx) ; 0.xx | | |
| Required rescue analgesia, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Final pain score below 4/10, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| Patient global impression of change, N (%) | | | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| Very much improved | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | | | | |
| Much improved | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | | | | |
| Minimally improved | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | | | | |
| No change | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | | | | |
| Minimally worse | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | | | | |
| Much worse | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | | | | |
| Very much worse | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | | | | |

Percentages are based within each column

**Table 31: Rescue analgesia and other treatments characteristics**

| | | Ketamine | Morphine | Total |
|---|---|---|---|---|
| Required rescue analgesia | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Required adjunctive analgesia | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Type of analgesia | Entonox | N (xx%) | N (xx%) | N (xx%) |
| | Paracetamol | N (xx%) | N (xx%) | N (xx%) |
| | Ibuprofen | N (xx%) | N (xx%) | N (xx%) |
| | Other | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Midazolam administered | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Midazolam dose | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |

| | | | | |
|---|---|---|---|---|
| Naloxone administered | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Naloxone dose | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Final pain score below 4/10 | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Participant sustained IMP overdose | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Participant sustained IMP underdose | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |

Percentages are based within each column

**Table 32: Ambulance vital signs characteristics of all randomised participants by treatment arm**

| Vital Signs | | Ketamine | Morphine | Total |
|---|---|---|---|---|
| Blood pressure Systolic (mmHg) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Blood pressure Diastolic (mmHg) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Pulse rate (bpm) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Respiration rate (bpm) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Oxygen sats (%) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Glasgow coma scale (GCS) eye | 1 | N (xx%) | N (xx%) | N (xx%) |
| | 2 | N (xx%) | N (xx%) | N (xx%) |
| | 3 | N (xx%) | N (xx%) | N (xx%) |
| | 4 | N (xx%) | N (xx%) | N (xx%) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Glasgow coma scale (GCS) motor | 1 | N (xx%) | N (xx%) | N (xx%) |
| | 2 | N (xx%) | N (xx%) | N (xx%) |
| | 3 | N (xx%) | N (xx%) | N (xx%) |
| | 4 | N (xx%) | N (xx%) | N (xx%) |
| | 5 | N (xx%) | N (xx%) | N (xx%) |
| | 6 | N (xx%) | N (xx%) | N (xx%) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| | 1 | N (xx%) | N (xx%) | N (xx%) |

| | | | | |
|---|---|---|---|---|
| Glasgow coma scale (GCS) verbal | 2 | N (xx%) | N (xx%) | N (xx%) |
| | 3 | N (xx%) | N (xx%) | N (xx%) |
| | 4 | N (xx%) | N (xx%) | N (xx%) |
| | 5 | N (xx%) | N (xx%) | N (xx%) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Glasgow coma scalw (GCS) total | 3 | N (xx%) | N (xx%) | N (xx%) |
| | 4 | N (xx%) | N (xx%) | N (xx%) |
| | 5 | N (xx%) | N (xx%) | N (xx%) |
| | 6 | N (xx%) | N (xx%) | N (xx%) |
| | 7 | N (xx%) | N (xx%) | N (xx%) |
| | 8 | N (xx%) | N (xx%) | N (xx%) |
| | 9 | N (xx%) | N (xx%) | N (xx%) |
| | 10 | N (xx%) | N (xx%) | N (xx%) |
| | 11 | N (xx%) | N (xx%) | N (xx%) |
| | 12 | N (xx%) | N (xx%) | N (xx%) |
| | 13 | N (xx%) | N (xx%) | N (xx%) |
| | 14 | N (xx%) | N (xx%) | N (xx%) |
| | 15 | N (xx%) | N (xx%) | N (xx%) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |

Percentages are based within each column

**Table 33: Ambulance vital signs study outcomes, [mean(sd)]**

| | Ketamine | Morphine | Unadjusted estimate (95% CI); p-value | Adjusted estimate (95% CI)*; p-value |
|---|---|---|---|---|
| Blood pressure Systolic (mmHg) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x) | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Blood pressure Diastolic (mmHg) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x) | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Pulse rate (bpm) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x) | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Respiration rate (bpm) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x) | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Oxygen sats (%) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x) | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Glasgow coma scale (GCS) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx |

Percentages are based within each column

**Table 34: Expected adverse event of all randomised participants by treatment arm**

| | Ketamine | Morphine | Total |
|---|---|---|---|

| Experienced adverse event | | | N (xx%) | N (xx%) | N (xx%) |
|---|---|---|---|---|---|
| Airway | Vomiting | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Aspiration | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Advanced airway management | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| Respiratory | Desaturation | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Need for ventilatory support | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| Cardiovascular | Arrhythmia | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Hypotension | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Hypertension | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| Neurologic | Sedation | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Excitatory movements | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Adverse behavioural reactions | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| Other | Allergic reaction | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Nausea | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |

Percentages are based within each column

**Table 35: Incidence of side effects and adverse events study outcomes, [N/total (%)]**

| | Ketamine | Morphine | Unadjusted estimate (95% CI); p-value | Adjusted estimate (95% CI)*; p-value | Unadjusted Differenc | Adjusted Difference (95% CI) |
|---|---|---|---|---|---|---|

| | | | | | | e (95% CI) | |
|---|---|---|---|---|---|---|---|
| Experienced adverse event | | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| Airway | Vomiting | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| | Aspiration | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| | Advanced airway management | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| Respiratory | Desaturation | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| | Need for ventilatory support | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| Cardiovascular | Arrhythmia | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| | Hypotension | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| | Hypertension | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| Neurologic | Sedation | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| | Excitatory movements | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| | Adverse behavioural reactions | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| Other | Allergic reaction | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| | Nausea | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |

Percentages are based within each column

**Table 36: Ambulance resource use for all randomised participants by treatment arm**

| | | Ketamine | Morphine | Total |
|---|---|---|---|---|
| Ambulance job cycle time | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Cumulative IMP dose | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Total | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |

| | | | | |
|---|---|---|---|---|
| Number of paramedics | Mean (sd)<br>Median (IQR)<br>Missing | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | N (xx%) | N (xx%) | N (xx%) |
| Number of ambulance clinicians | Total | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Mean (sd)<br>Median (IQR)<br>Missing | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | N (xx%) | N (xx%) | N (xx%) |
| Number of ambulance technicians/students | Total | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Mean (sd)<br>Median (IQR)<br>Missing | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | N (xx%) | N (xx%) | N (xx%) |
| Number of doctors | Total | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Mean (sd)<br>Median (IQR)<br>Missing | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | N (xx%) | N (xx%) | N (xx%) |
| Number of others attending | Total | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Mean (sd)<br>Median (IQR)<br>Missing | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | N (xx%) | N (xx%) | N (xx%) |

Percentages are based within each column

**Table 37: Resource use during ambulance journey study outcomes**

| | Ketamine | Morphine | Unadjusted estimate (95% CI); p-value | Adjusted estimate (95% CI)*; p-value |
|---|---|---|---|---|
| Ambulance job cycle time, median (IQR) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | HR, x.xx (x.xx to x.xx) ; 0.xx | HR, x.xx (x.xx to x.xx) ; 0.xx |
| Cumulative IMP dose, mean(sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Number of paramedics, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Number of ambulance clinicians, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Number of ambulance technicians/students, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Number of doctors , mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |

| | | | | |
|---|---|---|---|---|
| Number of others attending, mean (sd) | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |

Percentages are based within each column

**Table 38: Hospital stay and procedures for all randomised participants by treatment arm**

| | | Ketamine | Morphine | Total |
|---|---|---|---|---|
| Length of stay in ED | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Patient admitted to hospital | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Admitted to critical care | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Days in receiving level 1/2 critical care | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Days in receiving level 3 critical care | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Days in receiving unknown level of critical care | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Discharge location | Normal residence | N (xx%) | N (xx%) | N (xx%) |
| | Rehabilitation service | N (xx%) | N (xx%) | N (xx%) |
| | Another acute hospital | N (xx%) | N (xx%) | N (xx%) |
| | Death in hospital | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Participant entered to TARN | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| CT Scan | Yes | N (xx%) | N (xx%) | N (xx%) |
| | No | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Number of CT scans per patient | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |

Percentages are based within each column

**Table 39: Resource use at hospital study outcomes**

| | Ketamine | Morphine | Unadjusted estimate (95% CI); p-value | Adjusted estimate (95% CI)*; p-value | Unadjusted Difference (95% CI) | Adjusted Difference (95% CI) |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| Length of stay in ED, median (IQR) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | HR, x.xx (x.xx to x.xx) ; 0.xx | HR, x.xx (x.xx to x.xx) ; 0.xx | | |
| Patient admitted to hospital, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| Admitted to critical care, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| Days in receiving level 1/2 critical care, mean (sd) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx | | |
| Days in receiving level 3 critical care, mean (sd) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx | | |
| Days in receiving unknown level of critical care, mean (sd) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx | | |
| Length of stay hospital, mean (sd) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx | | |
| Participant entered to TARN, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| CT Scan use, N (%) | (n=xxx) xxx (xx.x%) | (n=xxx) xxx (xx.x%) | OR, x.xx (x.xx to x.xx) ; 0.xx | OR, x.xx (x.xx to x.xx) ; 0.xx | Xx (xx to xx) | Xx (xx to xx) |
| Number of CT scans per patient, mean (sd) | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx | | |

Percentages are based within each column

**Table 40: Longer term outcomes for all randomised participants by treatment arm at 3 month follow up**

| | Ketamine | Morphine | Total |
|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Pain severity | Overall | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Worst pain | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Least pain | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Average pain | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Pain now | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| Pain interference | | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |

Percentages are based within each column

**Table 41: Study outcomes at 3 month follow up, [mean(sd)]**

| | | Ketamine | Morphine | Unadjusted estimate (95% CI); p-value | Adjusted estimate (95% CI)*; p-value |
|---|---|---|---|---|---|
| Pain severity | Overall | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| | Worst pain | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| | Least pain | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| | Average pain | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| | Pain now | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Pain interference | | (n=xxx)<br>xx.x (xx.x) | (n=xxx)<br>xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x); 0.xx |

Percentages are based within each column

**Table 42: Longer term outcomes for all randomised participants by treatment arm at 6 month follow up**

| | Ketamine | Morphine | Total |
|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Pain severity | Overall | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Worst pain | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Least pain | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Average pain | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Pain now | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| Pain interference | | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |

Percentages are based within each column

**Table 43: Study outcomes at 6 month follow up, [mean(sd)]**

| | | Ketamine | Morphine | Unadjusted estimate (95% CI); p-value | Adjusted estimate (95% CI)*; p-value |
|---|---|---|---|---|---|
| Pain severity | Overall | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| | Worst pain | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| | Least pain | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| | Average pain | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| | Pain now | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |
| Pain interference | | (n=xxx) xx.x (xx.x) | (n=xxx) xx.x (xx.x) | MD, xx.x (xx.x to xx.x); 0.xx | MD, xx.x (xx.x to xx.x) ; 0.xx |

Percentages are based within each column

**Table 44: Baseline demographic characteristics of all randomised participants by treatment arm**

| Baseline demographics | | Ketamine | Morphine | Total |
|---|---|---|---|---|
| Age | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |

| | | | | |
|---|---|---|---|---|
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |
| Gender | Male | N (xx%) | N (xx%) | N (xx%) |
| | Female | N (xx%) | N (xx%) | N (xx%) |
| | Transgender | N (xx%) | N (xx%) | N (xx%) |
| | Other | N (xx%) | N (xx%) | N (xx%) |
| | Not disclosed | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Ethnicity | White | N (xx%) | N (xx%) | N (xx%) |
| | Black | N (xx%) | N (xx%) | N (xx%) |
| | Mixed | N (xx%) | N (xx%) | N (xx%) |
| | Any other ethnic group | N (xx%) | N (xx%) | N (xx%) |
| | Asian | N (xx%) | N (xx%) | N (xx%) |
| | Ethnicity not given | N (xx%) | N (xx%) | N (xx%) |
| | Missing | N (xx%) | N (xx%) | N (xx%) |
| Weight | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) | N (xx%) |

Percentages are based within each column

**Table 45: Injury characteristics of all randomised participants by treatment arm**

| | | | Ketamine | Morphine | Total |
|---|---|---|---|---|---|
| Mechanism of Injury: | Blunt Trauma | | N (xx%) | N (xx%) | N (xx%) |
| | Penetrating Trauma | | N (xx%) | N (xx%) | N (xx%) |
| | Burn | | N (xx%) | N (xx%) | N (xx%) |
| | Missing | | N (xx%) | N (xx%) | N (xx%) |
| Injuries sustained: | Fracture/ dislocation | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Soft tissue injury | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Wound/ laceration | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| Body part/region injured: | Head | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Neck | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Chest & back | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Abdomen | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Pelvis | Yes | N (xx%) | N (xx%) | N (xx%) |

| | | | | | |
|---|---|---|---|---|---|
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Upper limbs | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |
| | Lower limbs | Yes | N (xx%) | N (xx%) | N (xx%) |
| | | No | N (xx%) | N (xx%) | N (xx%) |
| | | Missing | N (xx%) | N (xx%) | N (xx%) |

Percentages are based within each column

**Table 46: Initial vital signs of all randomised participants by treatment arm**

| | | Ketamine | Morphine |
|---|---|---|---|
| Blood pressure Systolic (mmHg) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) |
| Blood pressure Diastolic (mmHg) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) |
| Heart rate (bpm) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) |
| Respiration rate (bpm) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) |
| Oxygen sats (%) | Mean (sd) | xx.x (xx.x) | xx.x (xx.x) |
| | Median (IQR) | xx.x (xx.x – xx.x) | xx.x (xx.x – xx.x) |
| | Missing (%) | N (xx%) | N (xx%) |
| Glasgow coma scale (GCS) eye | 1 | N (xx%) | N (xx%) |
| | 2 | N (xx%) | N (xx%) |
| | 3 | N (xx%) | N (xx%) |
| | 4 | N (xx%) | N (xx%) |
| | Missing (%) | N (xx%) | N (xx%) |
| Glasgow coma scale (GCS) motor | 1 | N (xx%) | N (xx%) |
| | 2 | N (xx%) | N (xx%) |
| | 3 | N (xx%) | N (xx%) |
| | 4 | N (xx%) | N (xx%) |
| | 5 | N (xx%) | N (xx%) |
| | 6 | N (xx%) | N (xx%) |
| | Missing (%) | N (xx%) | N (xx%) |
| Glasgow coma scale (GCS) verbal | 1 | N (xx%) | N (xx%) |
| | 2 | N (xx%) | N (xx%) |
| | 3 | N (xx%) | N (xx%) |
| | 4 | N (xx%) | N (xx%) |
| | 5 | N (xx%) | N (xx%) |
| | Missing (%) | N (xx%) | N (xx%) |
| | 3 | N (xx%) | N (xx%) |

| | | | |
|---|---|---|---|
| Glasgow coma scalw (GCS) total | 4 | N (xx%) | N (xx%) |
| | 5 | N (xx%) | N (xx%) |
| | 6 | N (xx%) | N (xx%) |
| | 7 | N (xx%) | N (xx%) |
| | 8 | N (xx%) | N (xx%) |
| | 9 | N (xx%) | N (xx%) |
| | 10 | N (xx%) | N (xx%) |
| | 11 | N (xx%) | N (xx%) |
| | 12 | N (xx%) | N (xx%) |
| | 13 | N (xx%) | N (xx%) |
| | 14 | N (xx%) | N (xx%) |
| | 15 | N (xx%) | N (xx%) |
| | Missing (%) | N (xx%) | N (xx%) |

**Table 47: Analysis model estimates of treatment difference of primary outcome**

| | **Ketamine (N=xxx)** | **Morphine (N=xxx)** | Unadjusted estimate (95% CI); p-value | Adjusted estimate (95% CI)*; p-value |
|---|---|---|---|---|
| **Sum of pain intensity difference, mean (sd)** | | | | |
| **ITT model** | xx (xx) | xx (xx) | MD, x.xx (x.xx to x.xx); 0.xxx | MD, x.xx (x.xx to x.xx); 0.xx |
| **CACE model** | xx (xx) | xx (xx) | MD, x.xx (x.xx to x.xx); 0.xxx | MD, x.xx (x.xx to x.xx); 0.xx |
| **Pocock's Win Ratio using composite of SPID and death** | xx (xx) | xx (xx) | MD, x.xx (x.xx to x.xx); 0.xxx | MD, x.xx (x.xx to x.xx); 0.xx |

*Adjusted for ambulance service, age, gender, alternative parent analgesia prior to randomisation

**Table 48: Sub-group analyses of the Sum of pain intensity difference outcome**

| **Subgroups** | **Ketamine**<br><br>**N; mean(sd)** | **Morphine**<br><br>**N; mean(sd)** | **Effect estimate (95% CI)** | **Interaction effect (95% CI); p-value** |
|---|---|---|---|---|
| **Age** | | | | |
| 1 | | | | |
| 2 | | | | |
| **Gender** | | | | |
| 1 | | | | |
| 2 | | | | |

| **Alternative parenteral analgesia** | | | | |
|---|---|---|---|---|
| 1 | | | | |
| 2 | | | | |

**Table 49: Completeness of health economic data by follow-up visit for all randomised participants by treatment arm**

| | **Ketamine** | | **Morphine** | | **Total** | |
|---|---|---|---|---|---|---|
| | **n** | **(%, N)** | **n** | **(%, N)** | **n** | **(%, N)** |
| **Health status[1]** | | | | | | |
| EQ-5D Baseline (derived) | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) |
| EQ-5D 3 months | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) |
| EQ-5D 6 months | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) |
| EQ-5D All visits | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) |
| **Resource use[2]** | | | | | | |
| Inpatient | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) |
| Outpatient | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) |
| Community | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) |
| Personal social services | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) |
| Wider costs | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) | xxx | (xx.x%, xxx) |

1.EQ-5D-5L index score
2. Range shown (3M,6M)

**Table 50: Health status, resource use and cost (complete cases) for all randomised participants by treatment arm**

| | **Ketamine** | | **Morphine** | | **Total** | |
|---|---|---|---|---|---|---|
| | **mean** | **(SD)** | **mean** | **(SD)** | **mean** | **(SD)** |
| **Health status[1]** | | | | | | |
| EQ-5D Baseline | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| EQ-5D 3 months | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| EQ-5D 6 months | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| QALYs | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| **Resource use** (all visits) | | | | | | |
| Inpatient nights | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Outpatient visits | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| A&E Visits | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Community | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| GP surgery visits | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| GP home visits | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| GP telephone contacts | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| GP video/online contacts | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| District nurse contacts | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Social worker contacts | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Physiotherapy contacts | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Occupational therapy contacts | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Counsellor | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Psychologist | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Home help/carer | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Other community contacts | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Medication<br>Special Equipment<br>Wider costs | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| **Cost**[2] | | | | | | |
| A: Cost (study procedures) | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| B: Cost (NHS contacts) | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| C: Cost (Personal social services) | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Cost (Total, A+B+C) | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| | | | | | | |

1 EQ-5D-5L index score

2 Wider costs are not included in the analytic perspective, which includes only health service and personal social services costs

### Table 51: Cost-effectiveness results

| | | **Incremental cost (95%CI)** | **Incremental QALYs (95%CI)** | **ICER (95%CI)** | **p[1]** | **p[2]** | **NMB[1]** | **NMB[2]** |
|---|---|---|---|---|---|---|---|---|
| Base case | | | | | | | | |
| | Imputed costs and QALYs, baseline EQ-5D adjusted | | | | | | | |
| | | | | | | | | |
| Sensitivity analyses | | | | | | | | |
| 1 | Inclusion of societal costs | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| 2 | Complete case analysis | | | | | | | |
| | | | | | | | | |
| 3 | Base case: sub-group analyses specified in the SAP | | | | | | | |
| | | | | | | | | |
| 4 | Baseline utility assumptions changes | | | | | | | |
| | | | | | | | | |
| 5 | Cost per SPID point reduction | | | | | | | |
| | | | | | | | | |

[1] probability cost-effective or net monetary benefit if willing to pay £20,000/QALY. [2] probability cost-effective or net monetary benefit if willing to pay £30,000/QALY

**Figures**

Figure 3: Total participants recruited by paramedic experience level by ambulance service

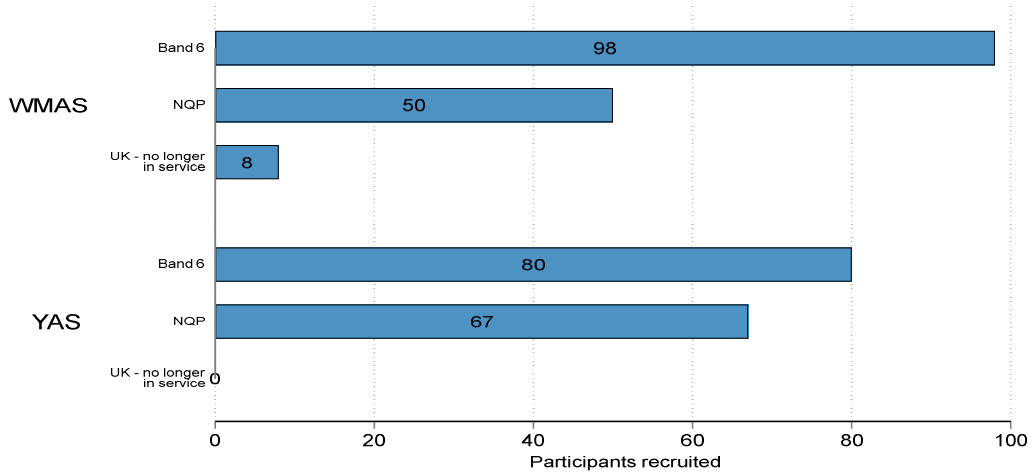


Figure 4: Trial trained paramedics by experience level by ambulance service

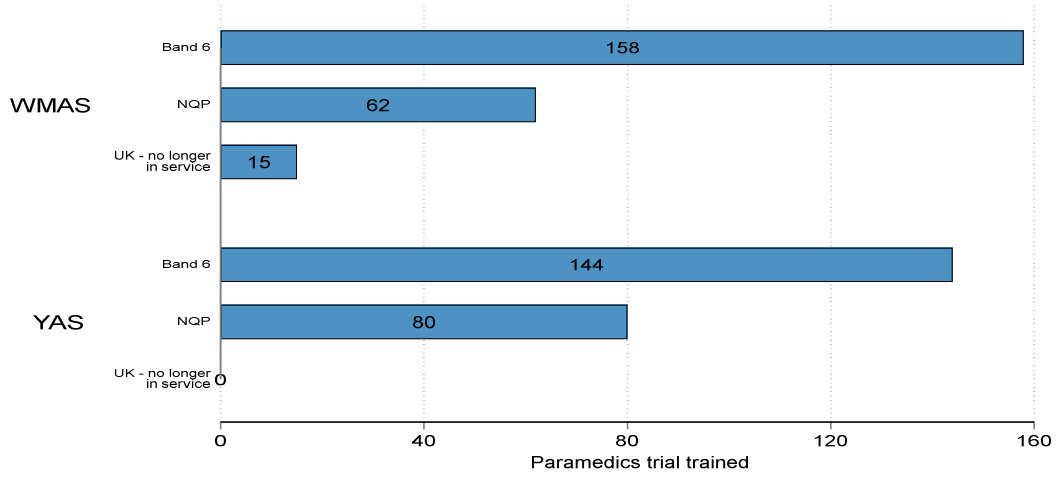


Figure 5: Percentage of participants recruited by paramedic experience for each ambulance service

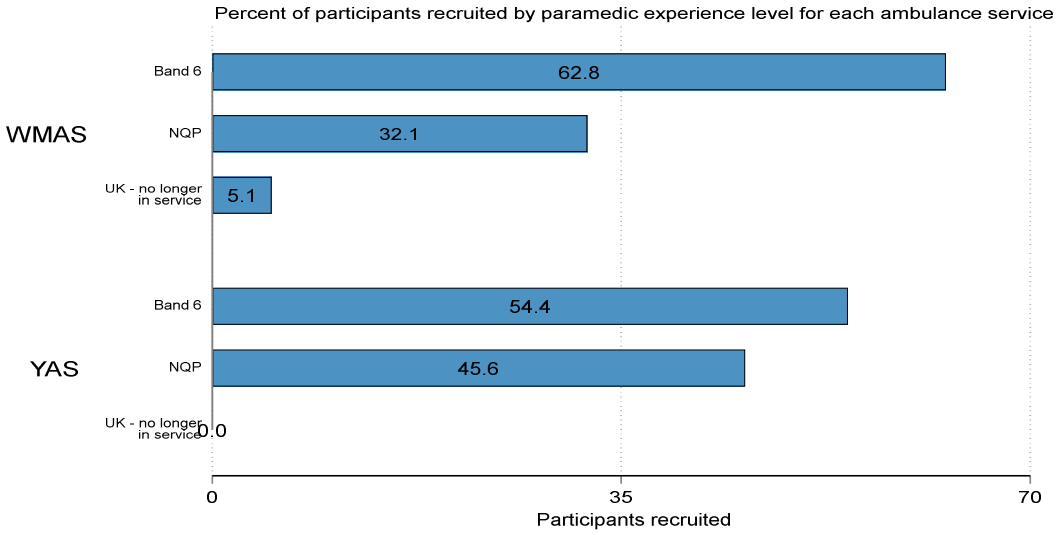


Figure 6: Percent of paramedics trial trained by experience level for each ambulance service.

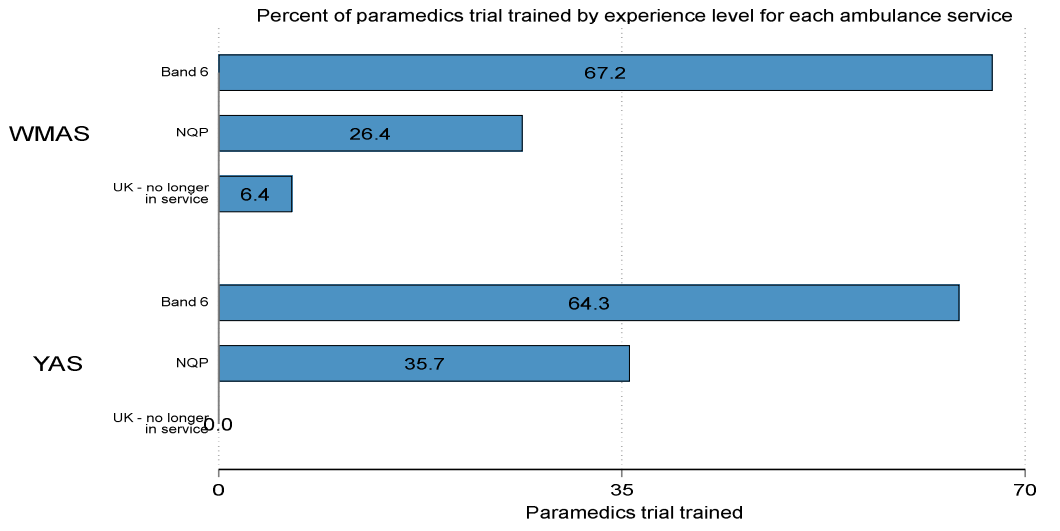

Figure 7a: Paramedic experience level percentages by ambulance service

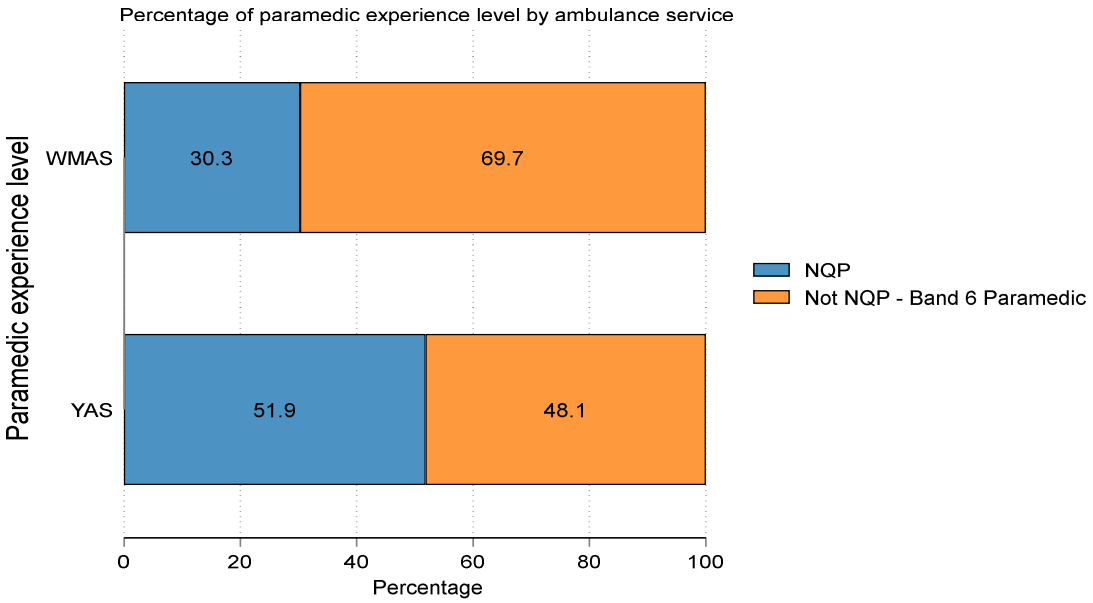


Figure 7b: Paramedic experience level percentages for all paramedics.

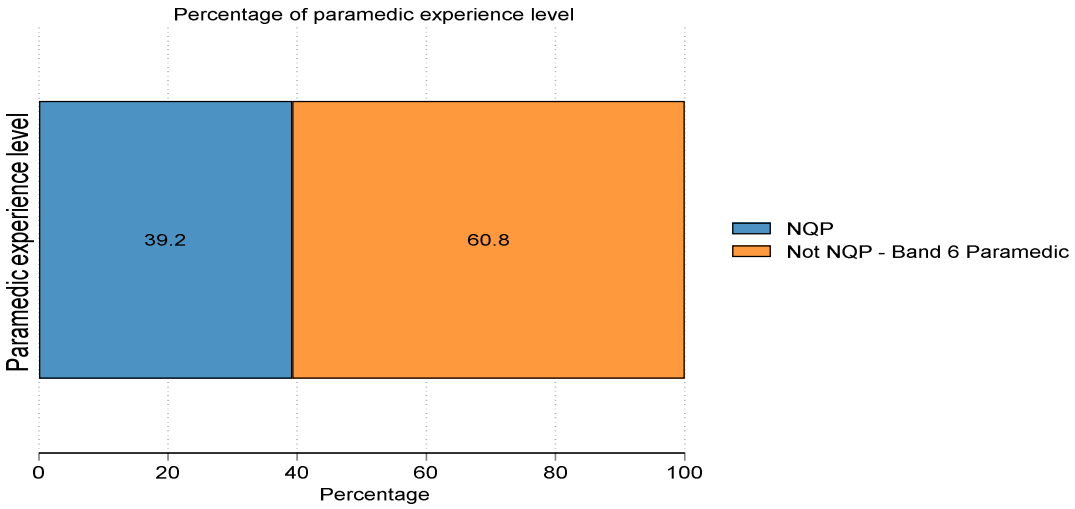


Figure 8: Adverse events by paramedic experience level

Figure 9: Non compliances by paramedic experience level

Figure 10: Proportion of participants experiencing adverse events by treatment arm and relative treatment arm difference as relative risk with 95% CI.

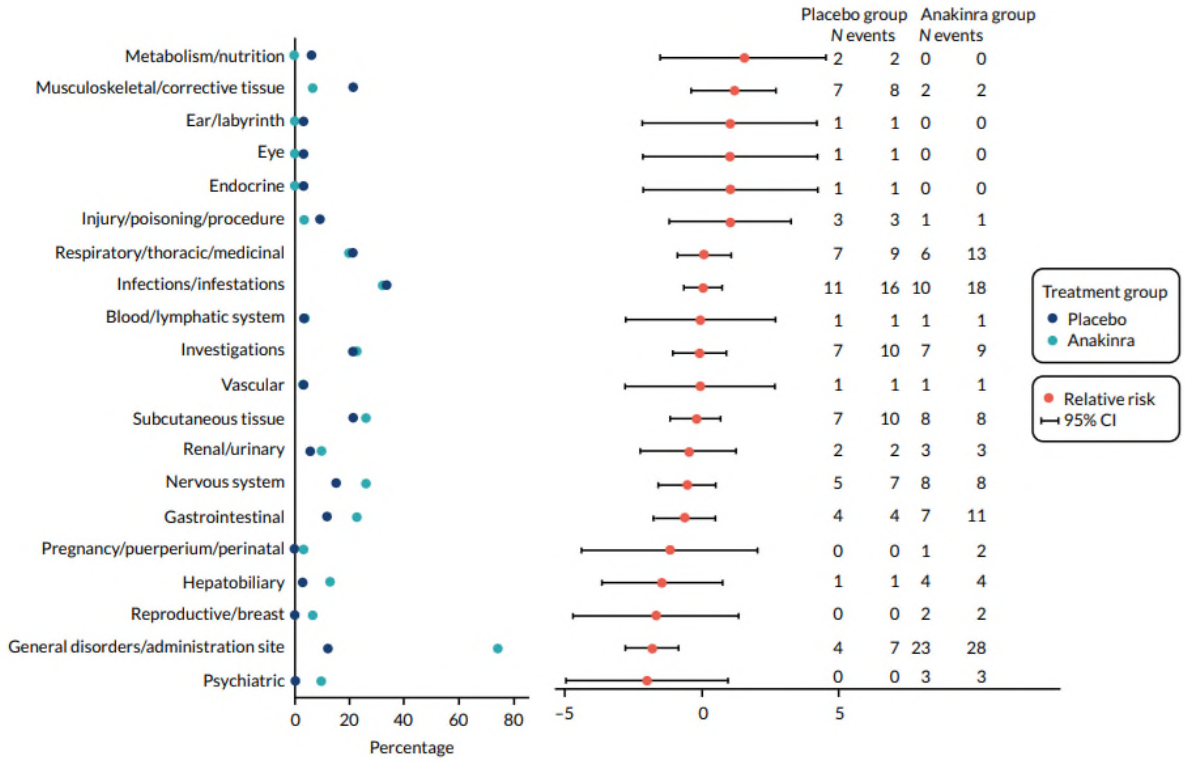


Figure 11: Graphical display of pain score over time summarised by treatment arm

Figure 12: Kaplan Meier plot for time to event outcomes

Figure 13: Dose response curve

Figure 14: Cost effectiveness Acceptability Curve (CEAC) showing the probability that the intervention is cost-effective across a range of cost-effectiveness thresholds.

Appendix 1: Mixed effect model outputs of vital signs and Glasgow coma scale

Variables used for adjusted model are defined as such
Agecat = 1 if age is <60, agecat =2 if age >=60
Asd_gender=1 if female, asd_gender=2 if male
Paracetamol = 1 if no paracetamol given as analgesia prior to randomisation, paracetamol = 2 if paracetamol given prior to randomisation

Appendix 1a: Unadjusted model output for respiration rate

```
Mixed-effects REML regression                   Number of obs     =      1,907
Group variable: tno                             Number of groups  =        394
                                                Obs per group:
                                                              min =          1
                                                              avg =        4.8
                                                              max =         13
                                                Wald chi2(1)      =       0.00
Log restricted-likelihood = -4114.6048          Prob > chi2       =     0.9522

------------------------------------------------------------------------------
pvs_respiratoryrate | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
--------------------+---------------------------------------------------------
           trialarm |
             Arm B  |  -.0190908   .3183001    -0.06   0.952    -.6429476    .6047659
              _cons |   18.60484    .222637    83.57   0.000     18.16848     19.0412
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
tno:                  (empty) |
-----------------------------+------------------------------------------------
Residual: AR(1)               |
                         rho |   .8613154   .0090987       .842386    .8781218
                      var(e) |   12.82894   .7455218      11.44788     14.3766
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 1905.00                   Prob > chi2 = 0.0000
```

Appendix 1b: Adjusted model outputs for respiration rate

```
Mixed-effects REML regression                   Number of obs     =      1,907
Group variable: tno                             Number of groups  =        394
                                                Obs per group:
                                                              min =          1
                                                              avg =        4.8
                                                              max =         13
                                                Wald chi2(4)      =       2.34
```

```
Log restricted-likelihood = -4113.6781          Prob > chi2       =     0.6729

------------------------------------------------------------------------------
pvs_respiratoryrate | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
--------------------+---------------------------------------------------------
           trialarm |
             Arm B  |  -.0417404   .3192342    -0.13   0.896    -.6674279    .5839471
          2.agecat  |  -.0830416   .3354906    -0.25   0.805     -.740591    .5745078
       2.asd_gender |   .4122983   .3288085     1.25   0.210    -.2321545    1.056751
      2.paracetamol |   .3125993   .4659268     0.67   0.502    -.6006005    1.225799
              _cons |   18.42936   .3631547    50.75   0.000     17.71759    19.14113
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
tno:                 (empty) |
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                         rho |   .8614311   .0091246      .8424436    .8782816
                      var(e) |   12.84127   .7494194      11.45332     14.3974
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 1897.91                   Prob > chi2 = 0.0000
```

Appendix 1c: Unadjusted model outputs for oxygen rate

```
Mixed-effects REML regression                   Number of obs     =      1,914
Group variable: tno                             Number of groups  =        395
                                                Obs per group:
                                                              min =          1
                                                              avg =        4.8
                                                              max =         13
                                                Wald chi2(1)      =       4.40
Log restricted-likelihood = -4319.5418          Prob > chi2       =     0.0359

------------------------------------------------------------------------------
pvs_oxygenrate | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
---------------+--------------------------------------------------------------
      trialarm |
        Arm B  |   .4854634   .2314357     2.10   0.036     .0318577    .9390691
         _cons |   96.59618   .1624591   594.59   0.000     96.27777     96.9146
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
tno:                 (empty) |
```

```
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                       rho |   .6930673   .0150728      .6623478    .7214602
                    var(e) |   8.974873   .4081214       8.20958    9.811505
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 1082.89                   Prob > chi2 = 0.0000
```

Appendix 1d: Adjusted model outputs for oxygen rate

```
Mixed-effects REML regression                   Number of obs     =      1,914
Group variable: tno                             Number of groups  =        395
                                                Obs per group:
                                                              min =          1
                                                              avg =        4.8
                                                              max =         13
                                                Wald chi2(4)      =      95.24
Log restricted-likelihood = -4279.7556          Prob > chi2       =     0.0000

------------------------------------------------------------------------------
pvs_oxygenrate | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
---------------+--------------------------------------------------------------
      trialarm |
        Arm B  |    .508935   .2129455     2.39   0.017     .0915696    .9263004
      2.agecat |  -1.832109   .2246709    -8.15   0.000    -2.272456   -1.391763
  2.asd_gender |   .5650903   .2192831     2.58   0.010     .1353033    .9948773
 2.paracetamol |   .2303191   .3219975     0.72   0.474    -.4007845    .8614226
         _cons |   97.38945     .24296   400.85   0.000     96.91325    97.86564
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
tno:                 (empty) |
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                       rho |   .6568152   .0162042      .6238814    .6874202
                    var(e) |   8.015194   .3529304      7.352472    8.737651
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 931.70                    Prob > chi2 = 0.0000
```

Appendix 1e: Unadjusted model output for heart rate

```
Mixed-effects REML regression                   Number of obs     =      1,961
Group variable: tno                             Number of groups  =        396
                                                Obs per group:
                                                              min =          1
                                                              avg =        5.0
```

```
                                                              max =         13
                                                Wald chi2(1)      =       0.30
Log restricted-likelihood = -7414.4142          Prob > chi2       =     0.5849

------------------------------------------------------------------------------
pvs_heartrate | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
--------------+---------------------------------------------------------------
     trialarm |
       Arm B  |  -.7248242   1.327059    -0.55   0.585    -3.325812    1.876164
        _cons |   81.58641   .9316761    87.57   0.000     79.76036    83.41246
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
tno:                 (empty) |
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                         rho |   .7966924   .0115647      .7728794    .8182646
                      var(e) |   252.2641   12.97784      228.0684    279.0268
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 1622.35                   Prob > chi2 = 0.0000
```

Appendix 1f: Adjusted model output for heart rate

```
Mixed-effects REML regression                   Number of obs     =      1,961
Group variable: tno                             Number of groups  =        396
                                                Obs per group:
                                                              min =          1
                                                              avg =        5.0
                                                              max =         13
                                                Wald chi2(4)      =       8.28
Log restricted-likelihood = -7406.3986          Prob > chi2       =     0.0818

------------------------------------------------------------------------------
pvs_heartrate | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
--------------+---------------------------------------------------------------
     trialarm |
       Arm B  |  -.6438985   1.322797    -0.49   0.626    -3.236533    1.948736
     2.agecat |  -3.018463   1.394566    -2.16   0.030    -5.751763   -.2851632
 2.asd_gender |   -3.02761   1.363022    -2.22   0.026    -5.699085   -.3561355
2.paracetamol |    .632973   1.955536     0.32   0.746    -3.199807    4.465753
        _cons |   84.71732   1.512028    56.03   0.000      81.7538    87.68084
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
```

```
-----------------------------+------------------------------------------------
tno:                  (empty) |
-----------------------------+------------------------------------------------
Residual: AR(1)               |
                         rho |   .7951445   .0116504      .7711567    .8168779
                      var(e) |   250.2783   12.88711      226.2528    276.8551
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 1610.34                   Prob > chi2 = 0.0000
```

Appendix 1g: Unadjusted model output for blood pressure systolic

```
Mixed-effects REML regression                   Number of obs     =      1,963
Group variable: tno                             Number of groups  =        396
                                                Obs per group:
                                                              min =          1
                                                              avg =        5.0
                                                              max =         13
                                                Wald chi2(1)      =       5.45
Log restricted-likelihood = -8420.6019          Prob > chi2       =     0.0195

------------------------------------------------------------------------------
pvs_bloodpressuresystolic | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
--------------------------+---------------------------------------------------
               trialarm |
                 Arm B  |   4.718615   2.020337     2.34   0.020     .7588267    8.678403
                  _cons |   142.3992   1.417528   100.46   0.000     139.6209    145.1775
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.      [95% conf. interval]
-----------------------------+------------------------------------------------
tno:                  (empty) |
-----------------------------+------------------------------------------------
Residual: AR(1)               |
                         rho |   .7599832   .0130589      .7331872    .7844228
                      var(e) |   622.0132   30.67074      564.7131    685.1275
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 1374.40                   Prob > chi2 = 0.0000
```

Appendix 1h: Adjusted model output for blood pressure systolic

```
Mixed-effects REML regression                   Number of obs     =      1,963
Group variable: tno                             Number of groups  =        396
                                                Obs per group:
                                                              min =          1
                                                              avg =        5.0
                                                              max =         13
                                                Wald chi2(4)      =      65.46
Log restricted-likelihood =  -8387.478          Prob > chi2       =     0.0000

------------------------------------------------------------------------------
pvs_bloodpressuresystolic | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
--------------------------+---------------------------------------------------
                trialarm |
                  Arm B  |     4.6648   1.911931     2.44   0.015     .9174836    8.412116
                2.agecat |    14.76394   2.020733     7.31   0.000     10.80337     18.7245
             2.asd_gender |   -.4444625   1.971826    -0.23   0.822    -4.30917    3.420245
            2.paracetamol |   -1.838434   2.852469    -0.64   0.519    -7.429171   3.752304
                    _cons |    133.8585   2.190186    61.12   0.000     129.5658    138.1512
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.      [95% conf. interval]
-----------------------------+------------------------------------------------
tno:                  (empty) |
-----------------------------+------------------------------------------------
Residual: AR(1)               |
                         rho |   .7401387   .0137664      .7119455    .7659498
                      var(e) |   573.3604   27.65366      521.6432    630.2051
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 1273.99                   Prob > chi2 = 0.0000
```

Appendix 1i: Unadjusted model output for blood pressure diastolic

```
Mixed-effects REML regression                   Number of obs     =      1,955
Group variable: tno                             Number of groups  =        395
                                                Obs per group:
                                                              min =          1
                                                              avg =        4.9
                                                              max =         13
                                                Wald chi2(1)      =       2.20
Log restricted-likelihood = -7548.0427          Prob > chi2       =     0.1381

------------------------------------------------------------------------------
--------
```

```
pvs_bloodpressurediastolic | Coefficient  Std. err.  z   P>|z|  [95% conf. interval]
---------------------------+-----------------------------------------------------
--------
                  trialarm |
                    Arm B  |    1.41135   .9518446  1.48   0.138  -.4542315 3.276931
                     _cons |   79.58655   .6680861  119.13 0.000  78.27713  80.89598
------------------------------------------------------------------------------
--------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
tno:                  (empty) |
-----------------------------+------------------------------------------------
Residual: AR(1)               |
                         rho |   .5793889   .0190089      .5409224    .6154366
                      var(e) |   183.5283   7.627245      169.1718    199.1031
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 624.73                Prob > chi2 = 0.0000
```

Appendix 1j: Adjusted model output for blood pressure diastolic

```
Mixed-effects REML regression                   Number of obs     =      1,955
Group variable: tno                             Number of groups  =        395
                                                Obs per group:
                                                              min =          1
                                                              avg =        4.9
                                                              max =         13
                                                Wald chi2(4)      =      11.75
Log restricted-likelihood = -7540.2694          Prob > chi2       =     0.0193

------------------------------------------------------------------------------
--------
pvs_bloodpressurediastolic | Coefficient  Std. err.  z   P>|z|  [95% conf. interval]
---------------------------+-----------------------------------------------------
--------
                  trialarm |
                    Arm B  |   1.466914   .9459209  1.55  0.121  -.387057   .320885
                 2.agecat  |  -2.539433   1.003141  -2.53 0.011  -4.505553 -.5733123
             2.asd_gender  |   1.035142   .9765654  1.06  0.289  -.8788909  2.949175
            2.paracetamol  |  -.4914691   1.431659  -0.34 0.731  -3.297469  2.314531
                     _cons |   80.68343   1.088141  74.15 0.000  78.55071   82.81615
------------------------------------------------------------------------------
--------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
tno:                  (empty) |
```

```
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                         rho |   .5748942   .0192176      .5360119    .6113427
                      var(e) |   181.7909   7.554034      167.5722    197.2162
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 607.48                Prob > chi2 = 0.0000
```

Appendix 1k: Unadjusted model output for Glasgow coma scale

```
Mixed-effects REML regression                   Number of obs     =      1,904
Group variable: tno                             Number of groups  =        392
                                                Obs per group:
                                                              min =          1
                                                              avg =        4.9
                                                              max =         13
                                                Wald chi2(1)      =       0.00
Log restricted-likelihood =  277.00011          Prob > chi2       =     0.9521

------------------------------------------------------------------------------
     pvs_gcs | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
    trialarm |
      Arm B  |  -.0007553   .0125708    -0.06   0.952    -.0253935    .0238829
       _cons |   14.97031   .0086623  1728.21   0.000     14.95334    14.98729
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
tno:                 (empty) |
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                         rho |   .3071933   .0215648      .2643438    .3488323
                      var(e) |   .0470252   .0016205      .0439539    .0503111
------------------------------------------------------------------------------
LR test vs. linear model: chi2(1) = 184.61                Prob > chi2 = 0.0000
```

Appendix 1l: Adjusted model output for Glasgow coma scale

```
Mixed-effects REML regression                   Number of obs     =      1,904
Group variable: tno                             Number of groups  =        392
                                                Obs per group:
                                                              min =          1
                                                              avg =        4.9
                                                              max =         13
                                                Wald chi2(4)      =       9.46
Log restricted-likelihood =  271.78157          Prob > chi2       =     0.0505
```

| pvs_gcs | Coefficient | Std. err. | z | P>\|z\| | [95% conf. | interval] |
|---|---|---|---|---|---|---|
| trialarm | | | | | | |
| Arm B | -.0001736 | .0125264 | -0.01 | 0.989 | -.0247249 | .0243777 |
| 2.agecat | -.032118 | .0132914 | -2.42 | 0.016 | -.0581687 | -.0060673 |
| 2.asd_gender | .0127708 | .0129694 | 0.98 | 0.325 | -.0126487 | .0381902 |
| 2.paracetamol | -.0172589 | .0187587 | -0.92 | 0.358 | -.0540252 | .0195074 |
| _cons | 14.98584 | .0143251 | 1046.13 | 0.000 | 14.95776 | 15.01392 |