Randomised controlled trial of the clinical and cost-effectiveness of cervical spine immobilisation following blunt trauma (SIS trial)

STATISTICAL ANALYSIS PLAN

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Contents

1. ADMINISTRATIVE INFORMATION

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2. INTRODUCTION

2.1 Background and rationale

Every year, approximately 80,000 patients in the UK and 5 million in the USA undergo cervical spine (c-spine) immobilisation with cervical collars due to suspected spinal injuries [1]. However, the number of patients who are ultimately diagnosed with significant cervical vertebral or spinal cord injuries (SCI) is much lower. In 2017, data from the Trauma Audit & Research Network (TARN) indicated that 5,476 patients were recorded as having sustained a cervical spine injury, with only about one-third (n=1,376) diagnosed with an SCI. This suggests that a large proportion of patients undergo immobilisation unnecessarily, exposing them to potential discomfort and complications without clinical benefit.

Most civilian trauma cases involve blunt mechanisms (e.g., falls and road traffic collisions), where accurately assessing spinal injury is challenging. In unconscious patients, precise injury assessment is often impossible, and even in conscious patients, distinguishing between whiplash-associated muscle injuries and unstable spinal fractures can be difficult. Consequently, even with the National Institute for Health and Care Excellence (NICE) decision rule [2], many patients are immobilised as a precaution. In most cases, spinal injuries are ruled out through assessment or imaging in the emergency department (ED), allowing removal of immobilisation within hours. However, in comatose patients with concomitant brain injuries, ruling out an unstable cervical spine fracture may take much longer. Previous studies have estimated that 2-4% of major trauma patients have significant cervical spine injuries after imaging. An analysis of TARN data from 1998-2009 found that 2.3% of major trauma patients had a significant cervical spine fracture or dislocation, while 0.8% had an SCI diagnosed before hospital discharge [3]. The expansion of TARN to all trauma-receiving hospitals and improved access to imaging have led to an increase in the median age of major trauma patients (current median age is 59 years old). The most recent 2017 analysis suggests that the true prevalence of potentially unstable cervical spine injuries and SCI in major trauma patients has increased to 6% and 1.8%, respectively. In older populations, spinal cord contusions without fracture, such as central cord syndrome, are also more common.

For the past two decades, spinal immobilisation has been a standard component of pre-hospital care for suspected spinal injuries [4]. However, the traditional "triple immobilisation" approach—including a cervical collar, head blocks, and tape/straps —has been associated with potential harms, particularly in patients with conditions such as ankylosing spondylitis, where forced immobilisation can lead to neurological deterioration [5,6]. The natural progression of SCI often involves worsening neurological deficits due to spinal cord contusions, which may be mistakenly attributed to inadequate

immobilisation. Beyond the direct costs of cervical collars (~£500,000 per year in the UK), the complications associated with unnecessary immobilisation contribute to significant healthcare and medico-legal expenses [7].

There is growing debate regarding the benefits of routine cervical immobilisation [8,9]. Several ambulance services in Scandinavia and Australia have reduced use of cervical collars without apparent increase in complications. This is known as "movement minimisation", which involves the use of head blocks or rolled blankets to reduce movement in the coronal plane, with the option for patients to sit upright if clinically appropriate. However, robust evidence is required to determine whether movement minimisation is non-inferior (i.e. not worse) to triple immobilisation before widespread adoption in the NHS, given the substantial personal, healthcare, and medico-legal consequences of SCI [10].

To address these concerns and provide a definitive answer regarding whether movement minimisation is non-inferior to triple immobilisation in patients with potential cervical spine injuries, the National Institute for Health Research (NIHR) has commissioned the Spinal Immobilisation Study (SIS) trial (reference NIHR131430). This trial will compare the clinical and cost-effectiveness of movement minimisation versus the current NHS standard of triple immobilisation in patients with suspected cervical spine injuries.

2.2 Objectives

2.2.1 Primary objective

To determine whether movement minimisation is deemed non-inferior (i.e. not worse) compared to triple immobilisation in relation to functional outcome (as assessed by the Functional Independence Measure (FIM) Motor) at hospital discharge.

2.2.2 Secondary objective

Secondary objectives are to assess the effects of the immobilisation techniques on clinical, patient-centred and economic outcomes pre-hospital, in hospital (ICU and ward) and at 6 months (180 days) following randomisation.

Specifically, the effect of the two techniques used to immobilise patients will be assessed using the following outcomes:

- Pre-hospital analgesia;

- Functional Independence Measure Cognitive
- Neurological change (from the point of randomisation to hospital discharge);
- Mortality (at days 30, 90 and 180);
- Length of stay in critical care and hospital;
- Other interventions for c-spine injury;
- Quality of life, costs and resource utilization (6 months);
- Adverse events: pressure sores, aspiration pneumonia, intracranial hypertension

A further secondary objective is to conduct an internal pilot study to confirm the feasibility of the large-scale multi-centre trial.

3. STUDY METHODS

3.1 Trial design

SIS is a UK-wide, open-label, pragmatic, phase 3, multi-centre, randomized controlled, non-inferiority, clinical and cost-effectiveness trial, with blinded assessment of outcome during hospital stay and at 180 days, to determine the effectiveness of immobilisation regimes involving movement minimisation and triple immobilisation (current NHS practice) in patients with suspected cervical spine injury recruited in a pre-hospital setting.

Multiple UK ambulance services, who manage adults and children with traumatic injuries and have a proven track record of successful participation in clinical trials, will be included in the study. The main trial will be preceded by an internal pilot phase of 6 months duration. This will follow the same processes as the main trial, and all patients recruited during the pilot phase will be included in the final analysis. The pilot will take place in 2 ambulance services (and associated air ambulance services where appropriate) to confirm recruitment rates, protocol compliance and data collection.

- **Type of comparison:** non-inferiority
- **Intervention:** Movement minimisation (head blocks or rolled blankets to minimise movement in coronal plane, with the option to sit up, if desired and not contraindicated due to other reasons, on ambulance stretcher, no tape/straps on head or chin).
- **Comparator:** Triple immobilisation (hard collar, blocks and tape/straps)

3.2 Randomisation

Patients will be randomised on scene by the recruiting paramedic. A progressive web application (PWA) will be developed for randomisation. The PWA will confirm participant was eligible for immobilisation as per JRCALC guidelines prior to randomising with automatic date/time/location stamping and site and confirmation of age group (<16 and ≥ 16 years). The PWA will be developed by the Programming Team in Warwick and tested in the pilot phase.

Patients will be randomised in a ratio of 1:1 (movement minimisation: triple immobilisation) and stratified by clinical factors including age group (<16 and ≥ 16 years) and recruiting centre to ensure balance over the two intervention arms.

If the PWA system is unavailable, a remote randomisation system will be provided by WCTU/Imperial College. The remote randomisation telephone number will be provided to ambulance services in the Investigator Site Files.

3.3 Sample size

The sample size is based on a non-inferiority hypothesis, where our objectives are to demonstrate that the movement minimisation (intervention) is no worse than triple immobilisation (comparator), by a pre-specified small difference, δ, on the functional outcome (FIM-motor) score. Statistically, our null hypothesis is that the intervention is inferior to the comparator by δ, and the alternative is that the intervention is non-inferior to the comparator by amount δ.

The originally planned sample size was 8316 patients (4158 per arm), choosing δ as 2 points on the FIM-motor, and using a standard deviation of 25.93, 90% power and two-sided 5% significance level (with loss-to-follow-up rate of 15%) (see protocol v1.0 - v6.0).

Due to the challenging recruitment in the pilot phase, we expect a smaller sample size will be recruited. The sample size calculation is still based on a non-inferiority hypothesis, choosing δ as 3 points on the FIM-motor (as the difference that is clinically acceptable as a margin of non-inferiority between the interventions), then using a standard deviation of 21.46 (calculated using the pilot phase data), a lower power 80% and two-sided 5% significance level. The loss-to-follow-up rate was also updated from 15% to 20% (additional 5% LTFU due to national data opt-out). The new sample size is 2010 patients (1005 per arm).

The sample size was informed using the following parameters:

- **Non-inferiority margin:** Regulatory guidelines recommend defining the margin based on a review of historical evidence of the efficacy of the comparator [11,12]. The minimal clinically important difference (MCID) for the FIM-motor is not established for the spinal cord injury patients [13]. However, using data from acute stroke patients, the MCID = 22 points (for FIM total), 17 points (for FIM-motor) and 3 points (for FIM-cognition) subscale [14]. This would suggest that a MCID for the FIM-motor (over the total or subscale scores) can be taken to be at least 3 points. Beninato et al's research [15] also suggests that a 3-point non-inferiority margin can be considered for FIM-motor.
- **Type 1 error:** Using regulatory guidance from the EMA CHMP26 we specify a two-sided 0.05 level of significance (or one-sided 0.025). An alternative way of stating this requirement is that

the lower bound of the two-sided 95% confidence interval (or one-sided 97.5% interval) for the difference between active and placebo should be above zero.

- **Standard deviation:** A study conducted in 2 adult-major (level 1) trauma centres in Victoria, Australia (243 patients) provided the baseline data of FIM-motor in adults with a blunt mechanism of injury and an Injury Severity Score (ISS) on admission to the hospital of >15 [16]. This population is expected to closely resemble the population that will be included in our trial. This study found the median (IQR) for the FIM-motor to be 61 (44-79) at discharge. Using a conversion formula [17], we derive the standard deviation of 25.93 from these data. In another prospective study carried out in Australia, data was analysed on an in-patient rehabilitation of spinal cord injury group (no. of episodes= 3753) from 2003- 2012 [18]. The FMI-motor median (and IQR) at discharge was 76 (51-83), which equates to a standard deviation of 23.7. Using data on 9 patients (by end of December 2023), we have the SD of ~ 11 (with 95% CI (7.57 – 21.46)). Using the upper limit, as a conservative estimate of this we can take our standard deviation as 21.46.
- **Loss-to-follow up rate:** Using the TARN data approximately 10% of patients die prior to hospital discharge. The LTFU rate is set at 20% including 5% loss of primary outcome data at discharge and additional 5% due to national data opt-out.

3.4 Blinding

Treatment allocation will be concealed prior to randomisation. It is not possible to effectively mask treatments in this trial from ambulance staff. The effect of knowledge of treatment allocation will be minimised through the use of clinical protocols to guide treatments to reduce performance bias. We have selected objective outcomes wherever possible to limit detection bias. Furthermore, where possible outcome assessors for in-hospital and follow-up outcome measures will be blinded to the treatment allocation.

To limit attrition bias pre-hospital-based data will be assessed regarding process variables to ensure that these are balanced across treatment arms, where expected. If there is any indication of bias, we will aim to alert the sites and offer further protocol and trial training.

3.5 Timing of final analysis

The final analysis will be conducted when the primary and secondary outcome data are collected from all randomised patients.

3.6 Timing of outcome assessments

The primary outcome is measured at hospital discharge. Timing of secondary outcome measurements are listed in Table 1 (section 5.1.2).

4. MONITORING OF THE TRIAL

4.1 Operational (Logistical) monitoring of patients

4.1.1 Screening data

All eligible patients will be screened for eligibility by ambulance staff (paramedics, doctors, nurses and other healthcare professionals) whilst on scene. A screening log will be maintained at each recruiting site which will include data on the numbers of patients meeting exclusion criteria, and meeting inclusion criteria but not entered into the trial along with the reasons for non-enrolment.

4.1.2 Eligibility

Inclusion criteria

1. Out of hospital with treatment being provided by NHS Ambulance Service staff
2. Patient assessed & found to require spinal immobilisation according to NHS Ambulance guidelines
3. Any Glasgow Coma Score
4. Transfer planned to ED

Exclusion criteria

1. Patients not requiring spinal immobilisation according to NHS Ambulance guidelines
2. Patients in whom placing a collar is contraindicated (e.g. pre-existing deformity)

4.1.3 Recruitment

6 UK ambulance services have been selected to randomise patients into the trial.

- A CONSORT diagram showing the flow chart of patients recruited in the study will be illustrated in Appendix Figure 1.
- Randomisation balance by stratification variables (site and age group) will be summarised in Appendix Table 1.

4.1.4 Withdrawal/follow-up

Participants may be discontinued from the trial at any time without prejudice. Unless a participant explicitly withdraws their consent, they will be followed up wherever possible, and data collected as per the protocol until the end of the trial. If a participant withdraws consent, we will retain all data including personal identifiable information until the point of withdrawal unless the participant or consultee explicitly tell us not to.

Participants who are randomised, but subsequently found to be ineligible, will be included in the study analysis and all follow-up completed.

In the rare case where researchers have been unable to make contact with a participant or their consultee following enrolment, routine health data sources will continue to be used for data collection.

All withdrawals will be summarised using frequencies and percentages by treatment arm in Appendix Table 2. The status of patients in the study, from screening to the end of the study, as well as the follow-up rates, will be summarised by treatment status in Appendix Table 3.

4.1.5 Baseline patient characteristics

Baseline characteristics of patients will be summarised using mean, standard deviation (SD), median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. Number of observed and missing cases will also be reported. The baseline summary will be presented in Appendix Table 4. The outcome summary will be presented in Appendix Table 6-13.

4.1.6 Compliance and protocol deviation

Deviations from the clinical trial protocol and Good Clinical Practice (GCP) can occur. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. A violation is a failure to comply with or variance from GCP and/or the final approved protocol. This results from error, fraud or misconduct. These cases should be documented in the protocol non-compliance form for the trial and appropriate corrective and preventative actions taken. Deviations and violations will be included and considered when the clinical trial report is produced, as they may have an impact on the analysis of the data. Compliance with the study protocol will be monitored centrally during the pilot study, and throughout the trial, to ensure the interventions in the trial and other routine clinical care are conducted consistently. All non-compliances (excluding treatment non-compliance) will be summarised by treatment status in Appendix Table 17. Regarding treatment compliance, see section 4.2.2 for details.

4.1.7 Safety and Harms

Treatment related safety outcomes will be summarised. See section 6.6 for details.

4.1.8 Unblinding

Allocation unblinding during the trial will be summarised by treatment arm in Appendix Table 18.

4.2 Statistical monitoring during the trial

4.2.1 Assessment of Bias

Patient recruitment will be checked against the number of patients screened and patients met exclusion criteria. Details will be presented in Appendix Table 3.

The data on the characteristics of patients and clinical measurements at baseline (for assessment of bias) are reported to the Data Monitoring Committee (DMC) and trial team in the interim and final reports. The trial team assesses the blinded data and the DMC assesses these blinded and unblinded data for any variables that may exceed potential thresholds (as judged by the clinical experts).

4.2.2 Non-compliance and non-adherence

In addition to the protocol deviations and violations defined in section 4.1.6, the change of the administration of allocated treatment to non-allocated treatment will be summarised.

Treatment compliance means the form of immobilisation the participant had upon arrival to hospital is the same as allocated immobilisation form. Treatment cross-over means patients randomised to movement minimisation arm but were given triple immobilisation and vice versa.

Administration of non-allocated treatment and compliance will be summarised by treatment status in Appendix Table 5.

4.2.3 Statistical Interim analyses and stopping guidance

As outlined in the trial protocol, the timing and frequency of the interim analyses were to be discussed and agreed with the DMC members. The initial plan was to conduct one formal interim analysis upon reaching primary outcome data for 50% of the target sample size (around 1000 participants), with statistical stopping criteria defined using the O'Brien and Fleming stopping rules [19]. This approach was endorsed by the DMC.

However, the recruitment has been slower than anticipated, and the lost to follow-up is higher than expected. Both factors make it uncertain that we will reach this milestone within the planned recruitment timeframe. The recruitment projection using latest recruitment data is likely to be in the range of (1274, 1434). Depending on the chase of missing data, the number of participants with

available FIM scores at the end of the extension period is projected to be between 500 and just over 1,000. Even if we were able to get the sufficient data for the interim analysis, it is likely that this would occur close to the end of the extended recruitment period, by the time of scheduled DMC meeting.

In light of this, the trial team shared the updated recruitment projections and trial milestones with the DMC. Following review, on 03 September 2025 the DMC recommended that the interim analysis should be removed due to feasibility concerns.

Therefore, the interim analysis will not be conducted. This change means that the statistical power of the final analysis will not be affected.

5. CLINICAL OUTCOMES AND ANALYSIS DATASET

5.1 Outcome definitions

5.1.1 Primary outcome

Functional Independence Measurement motor (FIM-motor) score at hospital discharge [20,21], which measures the level of disability in terms of burden of care.

FIM-motor is comprised of 13 motor items. Each item rates the patient's level of disability on a scale from 1 to 7, with 1 representing total dependence and 7 describing complete independence without the need for an aid. FIM-motor score sums the patient's performance on each of the motor items and ranges from 13 (lowest motor function) to 91 (highest motor function).

5.1.2 Secondary outcomes

Effectiveness:

- FIM-motor score at 30 days and 180 days after randomisation at video clinic or follow up appointments
- FIM-total and cognition scores at discharge, 30 days and 180 days after randomisation at video clinic or follow up appointments
- American Spinal Injury Association (ASIA) Impairment Scale at discharge [22]
- Mortality (at days 30, 90 and 180)
- Further intervention for c-spine injury in the first 30 days or discharge (use of collar for > 2 weeks, halo brace, c-spine surgery)
- Discharge destination

- Pre-hospital analgesic requirements (from Ambulance PRF)

Health Care System benefit:

- Assessment of in-trial cost effectiveness
- Critical care unit length and level of stay
- Hospital length of stay
- Re-admissions to hospital

Utilisation of Resource use:

- Utilisation of community care resources after acute hospital discharge to 6 months after randomisation
- EQ-5D-5L/EQ-5D-Y at discharge, 30 days and 6 months [23]

Outcome data will be collected up to specific time points as shown below (Table 1). The Health Care System benefit outcomes and utilisation of community resources will be reported in the health economic analysis only.

Table 1: Summary of clinical outcome measures

OUTCOMES	TIME POINT	SUBJECTS	SCORING
Primary outcome			
FIM-Motor score at hospital discharge	Hospital discharge	Full analysis set	Continuous: sums the patient's performance on 13 motor items and ranges from 13 to 91 (higher score indicates more independent).
Secondary outcomes			
FIM-Motor score at 30 days	30 days post randomisation	Full analysis set	Continuous: sums the patient's performance on 13 motor items and ranges from 13 to 91 (higher score indicates more independent).
FIM-Motor score at 180 days	180 days post randomisation	Full analysis set	Continuous: sums the patient's performance on 13 motor items and ranges from 13 to 91 (higher score indicates more independent).
FIM-total score at discharge	Hospital discharge	Full analysis set	Continuous: FIM is an 18-item instrument measuring a person's level of disability in terms of burden of care. FIM-total score sums the patient's performance on 18 items and ranges from 18 to 126. (higher score indicates more independent).
FIM-total score at 30 days	30 days post randomisation	Full analysis set	Continuous: sums the patient's performance on 18 items and ranges from 18 to 126. (higher score indicates more independent).
FIM-total score at 180 days	180 days post randomisation	Full analysis set	Continuous: sums the patient's performance on 18 items and

			ranges from 18 to 126. (higher score indicates more independent).
FIM-cognition at discharge	Hospital discharge	Full analysis set	Continuous: sums the patient's performance on 5 cognition items and ranges from 5 to 35. (higher score indicates more independent).
FIM-cognition at 30 days	30 days post randomisation	Full analysis set	Continuous: sums the patient's performance on 5 cognition items and ranges from 5 to 35. (higher score indicates more independent).
FIM-cognition at 180 days	180 days post randomisation	Full analysis set	Continuous: sums the patient's performance on 5 cognition items and ranges from 5 to 35. (higher score indicates more independent).
ASIA Impairment Scale at discharge	Hospital discharge	Full analysis set	Ordinal: • Level A: Complete (no motor or sensory function is preserved) • Level B: Incomplete (Sensory function, but not motor function, is preserved below the neurologic level) • Level C: Incomplete (Motor function is preserved below the neurologic level, but more than half of the key muscles below the neurologic level have a muscle grade less than 3 (i.e., they are not strong enough to move against gravity).) • Level D: Incomplete (Motor function is preserved below the neurologic level, and at least half of the key muscles below the neurologic level have a muscle grade of 3 or more (i.e., the joints can be moved against gravity).) • Level E: Normal (Motor and sensory function are normal)
Survival at hospital discharge	Hospital discharge	Full analysis set	Binary: survived vs deceased
Survival at 30 days	30 days post randomisation	Full analysis set	Binary: survived vs deceased Time (day) to death in 30 days: mortality is the event; censors include survival to 30 days follow-up and survival to withdrawal.
Survival at 90 days	90 days post randomisation	Full analysis set	Binary: survived vs deceased Time (day) to death in 90 days: mortality is the event; censors include survival to 90 days follow-up and survival to withdrawal.

Survival at 180 days	180 days post randomisation	Full analysis set	Binary: survived vs deceased Time (day) to death in 180 days: mortality is the event; censors include survival to 180 days follow-up and survival to withdrawal.
Further intervention for c-spine injury in the first 30 days or discharge	Hospital discharge and 30 days post randomisation	Full analysis set	Categorical (ordinal): None, Immobilisation (soft collar, hard collar, traction, halo, other), Surgery (anterior fixation, posterior fixation, anterior and posterior fixation, other)
Discharge destination	Hospital discharge	Full analysis set, excluding patients who died in hospital	Categorical (nominal): Home, Community based support/care, Another hospital, Other.
Pre-hospital analgesic requirements	Before hospital admission	Full analysis set	Categorical (nominal): None, Paracetamol, Codeine, Morphine, Penthrox, Ketamine, Fentanyl, Other
Critical care unit level	During hospital stay	Full analysis set	Categorical (ordinal): Level 3 (ICU/ITU), Level 2 (HDU), Not admitted to critical care unit.
Critical care unit length of stay	During ICU/ITU/HDU stay	Full analysis set, excluding patients who were not admitted to critical care unit	Continuous: Length of stay is counted in days=critical care unit discharge date - randomisation date. The outcome will be reported for 1) those alive at critical care unit discharge, 2) all patients admitted to critical care Time (day) to death in critical care unit: mortality is the event; survival to discharge is the competing risk; censors include still in critical care at the end of trial and survival to withdrawal.
Hospital length of stay	During hospital stay	Full analysis set	Continuous: Length of stay is counted in days=hospital discharge/death date-randomisation date. The outcome will be reported for 1) those alive at hospital discharge, 2) all patients Time (day) to death in hospital: mortality is the event; survival to discharge is the competing risk; censors include still hospitalised at the end of trial and survival to withdrawal.

EQ-5D-5L/EQ-5D-Y visual analogue scale (VAS) score at hospital discharge	Hospital discharge	Full analysis set, excluding patients who died in hospital	Continuous: The VAS score ranges from 0 to 100. 0 represent worst imaginable health and 100 indicates best imaginable health.
EQ-5D-5L/EQ-5D-Y index score at hospital discharge	Hospital discharge	Full analysis set, excluding patients who died in hospital	Continuous: The UK index score is derived using the EQ-5D UK Crosswalk value sets. Values range from <0 to 1. 0 represents death and 1 indicates best health state. Negative values indicate health states worse than death.
EQ-5D-5L/EQ-5D-Y visual analogue scale (VAS) score at 30 days	30 days post randomisation	Full analysis set, excluding patients who died by 30 days	Continuous: The VAS score ranges from 0 to 100. 0 represent worst imaginable health and 100 indicates best imaginable health.
EQ-5D-5L/EQ-5D-Y index score at 30 days	30 days post randomisation	Full analysis set, excluding patients who died by 30 days	Continuous: The UK index score ranges from <0 to 1. 0 represents death and 1 indicates best health state. Negative values indicate health states worse than death.
EQ-5D-5L/EQ-5D-Y visual analogue scale (VAS) score at 6 months	180 days post randomisation	Full analysis set, excluding patients who died by 6 months	Continuous: The VAS score ranges from 0 to 100. 0 represent worst imaginable health and 100 indicates best imaginable health.
EQ-5D-5L/EQ-5D-Y index score at 6 months	180 days post randomisation	Full analysis set, excluding patients who died by 6 months	Continuous: The UK index score is derived using the EQ-5D UK Crosswalk value sets. Values range from <0 to 1. 0 represents death and 1 indicates best health state. Negative values indicate health states worse than death.

5.1.3 Safety outcomes

Adverse events (pressure sores, aspiration pneumonia, intracranial hypertension) and serious adverse events will be reported in Appendix Table 14, 15 and 16.

5.2 Analysis datasets

Usually there are two types of datasets used for the statistical analysis: (a) Observed and (b) Imputed.

5.2.1 Observed dataset

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

5.2.2 Imputed dataset

If there are missing FIM-motor score at hospital discharge, we will assess the missing mechanism.

1. For patients discharged directly from Emergency Department (ED), if they did not provide FIM score (primary outcome), we will impute these patients using the median score calculated from the patients who were discharged from ED and provided FIM score data.
2. For patients discharged soon (usually <=24 hours) after hospital admission, if they did not provide FIM score (primary outcome), we will impute these patients using the median score calculated from the patients who were discharged after hospital admission and provided FIM score data.
3. For patients discharged (usually >24 hours) after hospital admission, we will apply two imputation rules:
    a) With the assumption of missing at random (MAR), the missing data will be imputed using the Multiple Imputation by Chained Equations (MICE) method based on the patients who were discharged with a FIM score [24]. 10 imputation datasets will be generated. Baseline assessments will be used as imputation covariates. That is, only data with non-missing baseline assessments will be used.
    b) The missing data will be imputed using the MICE method based on the patients who were discharged with a FIM score regardless of the availability of baseline assessments.
4. Tipping point analysis: To assess the robustness of the imputation results under the missing not at random (MNAR) assumption, a tipping point analysis will be performed for the primary outcome [25]. This analysis will introduce a shift parameter (β) to systematically adjust the imputed FIM-Motor scores for participants with missing data. The treatment effect will be re-estimated, and the non-inferiority conclusion will be reassessed over the range of shift. The tipping point will be defined as the value of β at which the statistical conclusion changes. If the β value required to overturn the non-inferiority conclusion corresponds to a clinically implausible shift in FIM-Motor scores (e.g., a difference greater than what would reasonably be expected due to unobserved factors), the findings will be considered robust under the MAR or MNAR assumption. Conversely, if the tipping point occurs within a clinically plausible range, the robustness of the results may be questioned.

All imputed datasets will be analysed in a sensitivity analysis (Appendix Table 19).

6. STATISTICAL ANALYSIS AND ESTIMAND FRAMEWORK

6.1 STATISTICAL PRINCIPLES

6.1.1 General considerations

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.

6.1.2 Confidence intervals and P values

The primary outcome will be analysed for non-inferiority using a one-sided significance level of 2.5% [26]. The point estimate, corresponding 95% confidence interval (CI) and p-value will be reported. A one-sided p value < 0.025 is considered statistically significant.

Secondary outcomes will be analysed under a superiority framework using a two-sided significance level of 5%. For each test, the point estimate, 95% CI, and p-value will be reported. A two-sided p-value < 0.05 is considered statistically significant.

No adjustment for multiplicity as the interim analysis is dropped. Outcome data will be compared by treatment arms. Results will be reported as follows, unless stated otherwise: Odds ratio with 95% CI and p-value for categorical outcomes; mean difference with 95% CI and p-value for continuous outcomes; hazard ratio with 95% CI and p-value for time to event outcomes; incidence rate ratio with 95% CI and p-value for count outcomes.

6.2 ESTIMAND

<table>
<tr><th>Estimand attributes</th><th>Estimator</th></tr>
<tr><td colspan="2">Objective
The primary objective of this trial is to determine whether movement minimisation is deemed non-inferior (i.e. not worse) compared to triple immobilisation in relation to functional outcome (as assessed by the Functional Independence Measure Motor) at hospital discharge.</td></tr>
<tr><td colspan="2">Treatment conditions
• Intervention:
Movement minimisation (head blocks or rolled blankets to minimise movement in coronal plane, with the option to sit up, if desired and not contraindicated due to other reasons, on ambulance stretcher, no tape/straps on head or chin).
• Control:
Triple immobilisation (hard collar, blocks and tape/straps)</td></tr>
<tr><td>Target population
Patients with suspected cervical spine injuries in pre-hospital setting</td><td>Analysis set
All randomised patients (full analysis set), in their randomised groups, with follow up at hospital discharge.</td></tr>
</table>

Variable (primary outcome) Functional Independence Measure (FIM) Motor score at hospital discharge post randomisation	FIM-motor is comprised of 13 motor items. Each item rates the patient's level of disability on a scale from 1 to 7, with 1 representing total dependence and 7 describing complete independence without the need for an aid. FIM-motor score sums the patient's performance on each of the motor items and ranges from 13 (lowest motor function) to 91 (highest motor function).
Summary measure Mean difference in FIM-Motor score between the movement minimisation (intervention) and triple immobilisation (control) at hospital discharge	***Analysis approach*** Use linear regression with and without adjustment. A 95% confidence interval will be constructed for the treatment effect. Non-inferiority will be concluded if the CI lies entirely above −3 (non-inferiority margin).
Intercurrent events (ICE) • **ICE 1:** Treatment non-compliance • **ICE 2:** Death before hospital discharge • **ICE 3:** Consent not obtained before hospital discharge	***Strategies for handling ICEs:*** **ICE 1:** Hypothetical Strategy (Inverse Probability Weighting (IPW) analysis) **ICE 2:** Hypothetical Strategy (IPW analysis) **ICE 3:** Hypothetical Strategy (IPW analysis)

6.3 Main analysis

6.3.1 Primary analysis

Primary analysis will be based on full analysis set following ICH E9 guidelines [28]. All randomised participants will be included and analysed according to the treatment arm they were randomised to, irrespective of the treatment they actually received and regardless of whether they adhered to the protocol.

The primary outcome, the FIM-Motor score at hospital discharge, will be compared between the intervention group (movement minimisation) and the control group (triple immobilisation) using a linear regression model. The estimated mean difference (Intervention – Control) and corresponding 95% confidence interval (CI) will be reported.

The statistical hypotheses are as follows:

- Null hypothesis (H_0): μ (intervention) – μ (control) ≤ -3
- Alternative hypothesis (H_1): μ (intervention) – μ (control) > -3

Interpretation of the results will be based on the position of the 95% CI relative to the non-inferiority margin (−3), as outlined below (see Figure 1):

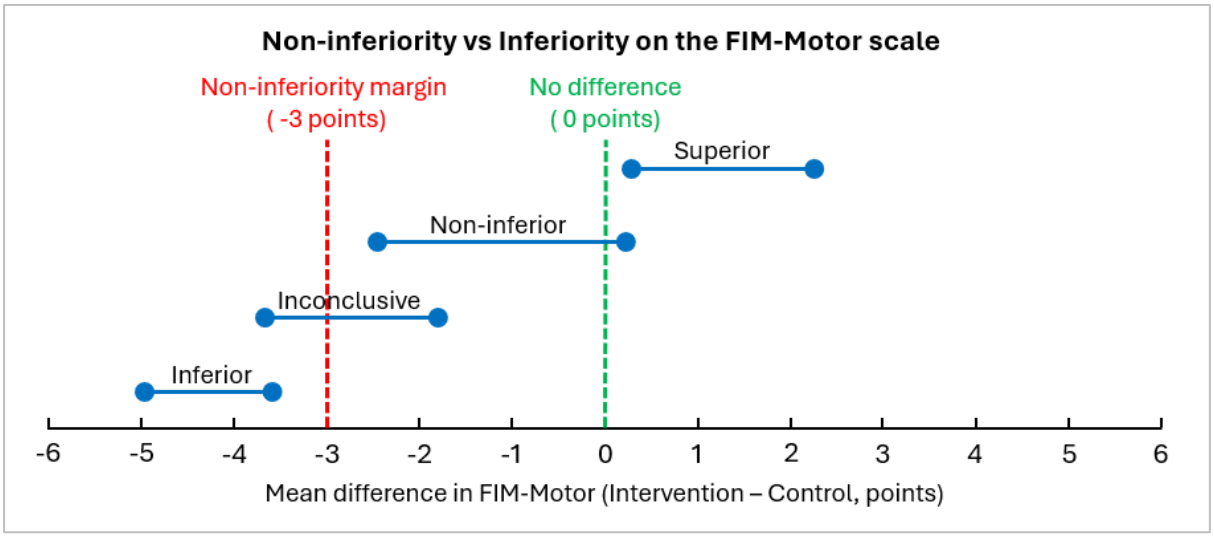
- If the 95% CI lies entirely above −3, we will reject H_0 and conclude that the intervention is non-inferior to the control.
- If the 95% CI lies entirely above 0, the intervention will be considered superior.
- If the 95% CI crosses −3, the result will be considered inconclusive and the null hypothesis (inferiority) is not rejected.
- If the 95% CI lies entirely below −3, the intervention will be considered inferior.

Model assumptions will be assessed visually (e.g. using residual plots) and, where appropriate, formally tested (e.g. the Anderson–Darling test for normality of residuals). If key assumptions are violated, suitable alternative analytical approaches will be considered (e.g. data transformation or non-parametric methods).

The primary analysis will be adjusted for important baseline covariates (age, gender and mechanism of injury) and stratification variable (site), which will be treated as fixed effects. The receiving hospital will be treated as a random effect.

The unadjusted estimate and the 95% CI will also be presented for the primary analysis.

Figure 1: Interpretation of the 95% Confidence Interval for the Mean Difference in FIM-Motor Score (Intervention – Control)



6.3.2 Sensitivity analysis (of primary outcome)

All imputed datasets will be analysed in a sensitivity analysis (see section 5.2.2 for details on imputation methods). The primary outcome will be re-analysed using the same unadjusted method as the primary ITT analysis. For the MICE model, bootstrap methods will be used to estimate the 95% CI.

Per protocol (PP) analysis will also be conducted to assess the robustness of conclusion of the primary analysis. The PP population will comprise the subset of participants from the full analysis set who adhered sufficiently to the trial protocol. This include patients who received the originally allocated intervention and had no treatment non-compliance or cross-over that are considered to affect the evaluation of efficacy, in accordance with the description of a "per-protocol set" in ICH E9 guidelines [27].

To account for ICEs, we will use Inverse Probability Weighting (IPW) approach [28]. Non-ICE probabilities will be estimated using a logistic regression model conditional on baseline covariates. Participants will then be reweighted by the inverse of these probabilities, with weights stabilized and extreme values truncated as needed to improve robustness. The weights will be applied in the outcome model to estimate the treatment effect. This approach provides unbiased estimates under the assumption that, conditional on the covariates, ICE is independent of the outcome. Bootstrap methods will be used to derive 95% confidence intervals for the IPW estimates.

All sensitivity analyses will be conducted both with and without adjustment for pre-specified covariates used in the primary analysis. The results will be summarised in Appendix Table 19.

6.3.3 Secondary analysis

Secondary analysis will be based on full analysis set following ICH E9 guidelines.

Secondary outcomes will be analysed under a superiority hypothesis using two-sided tests at the 5% significance level. A two-sided p-value <0.05 will be considered statistically significant.

The continuous secondary outcomes will be analysed using linear regression models, with and without adjustment. The estimated mean difference (Intervention – Control) and corresponding 95% CI will be reported. The statistical hypotheses are as follows:

- Null hypothesis (H_0): μ (intervention) – μ (control) = 0
- Alternative hypothesis (H_1): μ (intervention) – μ (control) ≠ 0

If the 95% CI for the mean difference does not include 0, the difference will be considered statistically significant in favour of the group with the higher mean.

The categorical outcomes will be analysed using logistic regression models, with and without adjustment. The estimated difference in proportions (Intervention – Control) and corresponding 95% CI will be reported. The statistical hypotheses are as follows:

- Null hypothesis (H_0): p (intervention) – p (control) = 0
- Alternative hypothesis (H_1): p (intervention) – p (control) ≠ 0

If the 95% CI for the proportion difference does not include 0, the difference will be considered statistically significant. Binary outcomes will be analysed using binary logistic regression model. Ordinal outcome will be analysed using ordinal logistic regression model, based on the proportional odds (PO) assumption. The PO assumption will be tested using the Brant test. If the assumption is violated, we will report the results of both PO and partial PO models as the PO model provides a useful estimation of the average treatment effect over the ordinal categories [29, 30]. Nominal outcomes will be analysed using nominal logistic regression model.

Time to event outcomes at fixed follow-up will be analysed using Kaplan-Meier plots without adjustment and Cox regression with adjustment. Hazard ratio (HR) with 95% CI and p value will be reported. The proportional hazard (PH) assumption will be assessed by visual inspection of the survival curves and by examining scatterplot of Schoenfeld residuals. If the PH assumption is violated, a time-varying coefficient model will be applied by including a treatment-by-time interaction term. For time to mortality in critical care and hospital, cumulative incidence function will be used. The HR with 95% CI and p value will be reported for the risk of mortality.

Covariates used for adjustment are the same as primary analysis.

6.3.4 Subgroup analysis

Exploratory sub-group analyses for primary outcome will be reported using 99% confidence intervals. Linear mixed effect regression will be used with interaction terms (treatment group by sub-group) to estimate sub-group effects. We will do the following subgroups analysis:

- Age <65 vs ≥65
- Mechanism of injury: Fall<2m vs other mechanisms
- Spinal pain/discomfort: 0-3 (mild) vs 4-6 (moderate) vs 7-10 (severe)

6.4 Missing data

Every effort will be made to minimise missing data for both baseline characteristics and outcomes. Missing data will be assessed carefully and reported transparently.

In this trial, death is rare and therefore is expected to contribute minimally to overall missingness. The primary source of missing data is anticipated to arise from patients being discharged before the site has an opportunity to obtain formal consent. To address this, an opt-out strategy has been adopted. For patients who were verbally assented at randomisation but have been lost following discharge (sites unable to consent), a participant information sheet (PIS) and opt-out form will be sent via post or email. If no opt out request is received, we will assume consent for the period of hospitalisation and the data from this will be included in the study.

All missing primary outcome will be imputed using the methods described in section 5.2.2. Analyses based on the imputed datasets will be conducted as sensitivity analyses, as outlined in section 6.3.2.

6.5 Harms

This trial is comparing two interventions that are already in routine use in NHS clinical practice, and as such, only those Adverse Events that are assessed as being serious will be collected on a Serious Adverse Event CRF. The frequency and causality of adverse events (AEs) and serious adverse events (SAEs) will be summarised and compared by treatment arm using incidence case analysis. Frequency and percentage of patients with at least one AE will be reported. Incidence rate with 95% CI and p value will be reported. Results will be reported in Appendix Table 14-16.

6.6 Statistical software

All statistical analyses will be carried out using SAS, Stata, or R. The use of any additional statistical software/packages will be reported in the final report.

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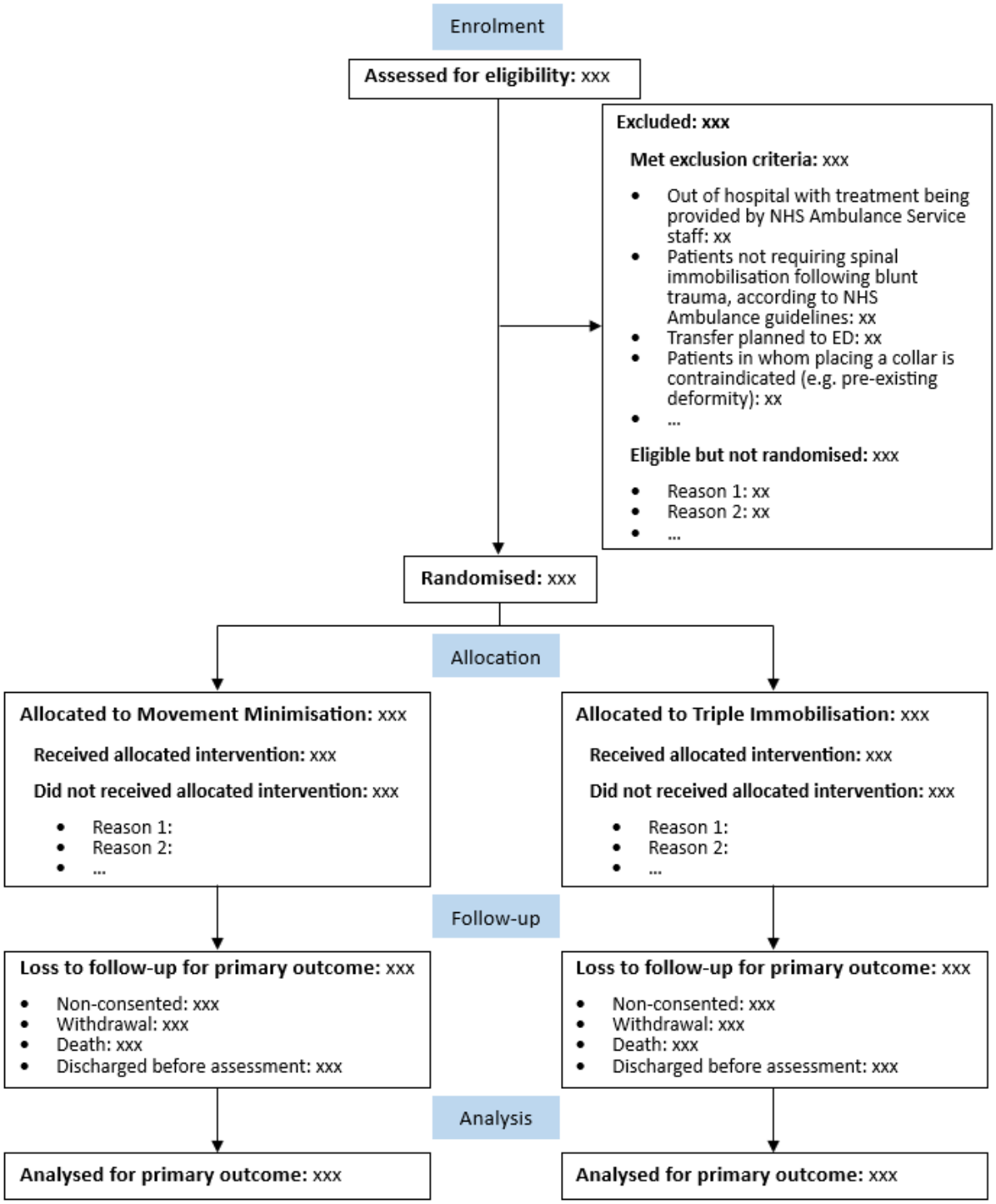
8. APPEDNDIX TABLES AND FIGURES

8.1 CONSORT

Figure 1: CONSORT diagram



8.2 Randomisation, baseline and intervention

Table 1: Randomisation balance by site and age group

		MM (N=)	TI (N=)	Total (N=)
Ambulance service	Site 1			
	Site 2			
	…			
Age Group	<16 years old			
	≥ 16 years old			
Overall balance				

Table 2: Summary of study withdrawal by treatment arm and total

		MM (N=)	TI (N=)	Total (N=)
Total number of withdrawals				
Withdrawal Type	Withdrawal from patient-reported outcomes but routine health data collection can continue			
	Withdrawal from any future data collection but data already collected can be retained			
	Withdrawal from any future data collection and removal of previously collected identifiable data			

Table 3: Patient flow by treatment arm and overall

	MM	TI	Total
Population	-	-	
Screened	-	-	
Exclusion criteria met	-	-	
Eligible but not randomised	-	-	
Randomised			
Admitted to ED			
Admitted to ICU			
Consent not obtained			
Withdrawn before hospital discharge			
- *Withdrawal from patient-reported outcomes but routine health data collection can continue*			
- *Withdrawal from any future data collection but data already collected can be retained*			
- *Withdrawal from any future data collection and removal of previously collected identifiable data*			
Hospital discharged alive			
Hospital discharged dead			
Not discharged from hospital yet			
Questionnaire received at hospital discharge			
Non-response to Questionnaire at hospital discharge			

30 days follow-up			
Reached 30 days follow-up			
• Consent not obtained			
• Patients withdrawn before 30 days follow-up			
- *Withdrawal from patient-reported outcomes but routine health data collection can continue*			
- *Withdrawal from any future data collection but data already collected can be retained*			
- *Withdrawal from any future data collection and removal of previously collected identifiable data*			
• Survived to 30 days			
• Deceased at 30 days			
• Questionnaire received at 30 days follow-up			
• Non-response to Questionnaire at 30 days follow-up			
90 days follow-up			
Reached 90 days follow-up			
• Consent not obtained			
• Withdrawn before 90 days follow-up			
- *Withdrawal from patient-reported outcomes but routine health data collection can continue*			
- *Withdrawal from any future data collection but data already collected can be retained*			
- *Withdrawal from any future data collection and removal of previously collected identifiable data*			
• Survived to 90 days			
• Deceased at 90 days			
180 days follow-up			
Reached 180 days follow-up			
• Consent not obtained			
• Patients withdrawn before 180 days follow-up			
- *Withdrawal from patient-reported outcomes but routine health data collection can continue*			
- *Withdrawal from any future data collection but data already collected can be retained*			
- *Withdrawal from any future data collection and removal of previously collected identifiable data*			
• Survived to 180 days			
• Deceased at 180 days			
• Questionnaire received at 180 days follow-up			
• Non-response to Questionnaire at 180 days follow-up			

Note: Percentages prior to randomisation used the total screened as the denominator.

Table 4: Baseline data by treatment arm and overall

		MM (N=)	TI (N=)	Total (N=)
Neurological impairment on scene, No. (%)	No			
	Yes*			
	Unable to assess			
	Missing			
If Yes, any movement in Right Arm	No			
	Yes			
	Missing			
If Yes, any movement in Left Arm	No			
	Yes			
	Missing			
If Yes, any movement in Right Leg	No			
	Yes			
	Missing			
If Yes, any movement in Left Leg	No			
	Yes			
	Missing			
If Yes, Sensory involvement – Right Arm	Absent			
	Altered			
	Normal			
	Not Testable			
	Missing			
If Yes, Sensory involvement – Left Arm	Absent			
	Altered			
	Normal			
	Not Testable			
	Missing			
If Yes, Sensory involvement – Right Leg	Absent			
	Altered			
	Normal			
	Not Testable			
	Missing			
If Yes, Sensory involvement – Left Leg	Absent			
	Altered			
	Normal			
	Not Testable			
	Missing			
Glasgow Coma Score** (The lower the score, the deeper the coma)	N			
	Median (IQR)			
	13-15 (mild), No. (%)			
	9-12 (moderate), No. (%)			
	3-8 (severe), No. (%)			
	Missing, No. (%)			

Spinal pain/discomfort (The higher the score, the more severe the pain/discomfort)	N			
	Median (IQR)			
	0-3 (mild), No. (%)			
	4-6 (moderate), No. (%)			
	7-10 (severe), No. (%)			
	Missing, No. (%)			
Age (years)	N			
	Mean (SD)			
	Median (IQR)			
	Range			
	Missing, No. (%)			
Gender, No. (%)	Female			
	Male			
	Missing			
Previous Diagnosis, No. (%)	Ankylosing spondylitis			
	Osteogenesis Imperfecta			
	Osteoporosis			
	Other bone conditions			
	None			
	Missing			
History of previous neurological impairment, No. (%)	No			
	Yes			
	Missing			
Alteration in neurology since injury, No. (%)	No			
	Yes			
	Not applicable			
	Missing			
Duration of immobilisation (up until arrival at hospital) (minutes)	N			
	Mean (SD)			
	Median (IQR)			
	Range			
	Missing, No. (%)			
Mechanism of injury, No. (%)	Fall <2m			
	Fall >2m			
	Road Traffic Collision - occupant			
	Road Traffic Collision - pedestrian			
	Road Traffic Collision - push bike			
	Road Traffic Collision - other			
	Sports injury			
	Assault			
	Other			

	Missing			

**These are patients reported altered/impaired sensation – numbness/paraesthesia etc.*

***GCS score: The highest possible GCS score is 15, and the lowest is 3. A score of 15 means you're fully awake, responsive and have no problems with thinking ability or memory. Generally, having a score of 8 or fewer means you're in a coma.*

Table 5: Treatment non-compliance and cross-over by treatment arm and overall

		MM (N=)	TI (N=)	Total (N=)
Treatment Compliance*, No. (%)	Yes			
	No			
	Missing			
Reason for treatment non-compliance, No. (%)	Irritability of participant			
	Unable to lie flat			
	Unable to tolerate immobilisation			
	To improve packaging			
	Other			
	Missing			
Treatment Cross-over**, No. (%)	Yes			
	No			
	Missing			

**'treatment compliance': The form of immobilisation the participant had upon arrival to hospital is the same as allocated immobilisation form.*

***'treatment cross-over': randomised to Treatment MM but given Treatment TI and vice versa.*

8.3 Primary Outcome Measure

Table 6: Treatment comparison of FIM-Motor score at hospital discharge

		MM	TI	Treatment difference (MM - TI)	Unadjusted treatment effect (Mean difference (95% CI, p value))	Adjusted treatment effect (Mean difference (95% CI, p value))
FIM-Motor Subtotal Score at hospital discharge (primary analysis (ITT))	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing, No. (%)					
	- Unobtainable					
	- Withdrawal					
FIM-Motor Subtotal Score at hospital discharge (Per protocol (PP))	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing, No. (%)					
	- Unobtainable					
	- Withdrawal					

Note: FIM-Motor is comprised of 13 motor items and each item rates the patient's level of disability on a scale from 1 to 7. The FIM motor score sums the patient's performance on each of the items and ranges from 13 (lowest motor function) to 91 (highest motor function). Higher score indicates more independent.

8.4 Secondary Outcome Measures

Table 7: FIM-Motor score at hospital admission, 30 days and 180 days, and FIM-Cognitive & FIM-Total score at hospital admission, hospital discharge, 30 days and 180 days

		MM	TI	Treatment difference (MM - TI)	Unadjusted treatment effect (Mean difference (95% CI))	Adjusted treatment effect (Mean difference (95% CI))
FIM-Motor Subtotal Score (Higher score indicates more independent)						
Hospital admission	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawal					
30 days	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawal					
180 days	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawal					
FIM-Cognitive Subtotal Score (Higher score indicates more independent)						
	N					

Hospital admission	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawal					
Hospital discharge	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawal					
30 days	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawal					
180 days	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawal					
FIM Total Score (Higher score indicates more independent)						
Hospital admission	N					
	Mean (SD)					
	Median (IQR)					
	Range					

	Missing					
	- Unobtainable					
	- Withdrawal					
Hospital discharge	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawal					
30 days	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawal					
180 days	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawal					

Table 8: ASIA Impairment Scale at hospital admission and discharge

		MM	TI	Treatment difference (MM- TI)	Unadjusted treatment effect (OR (95% CI))	Adjusted treatment effect (OR (95% CI))
Neurological impairment at	No					
	Yes					

hospital admission, No. (%)	Unable to assess					
	Missing					
ASIA at hospital admission, No. (%) (enabled only the previous question='Yes')	Grade A: Complete					
	Grade B					
	Grade C					
	Grade D					
	Grade E: Normal					
	Missing					
Neurological impairment at hospital discharge, No. (%)	No					
	Yes					
	Unable to assess					
	Withdrawal					
	Deceased in hospital					
	Missing					
ASIA at hospital discharge, No. (%) (enabled only the previous question='Yes')	Grade A: Complete					
	Grade B					
	Grade C					
	Grade D					
	Grade E: Normal					
	Missing					

Note: The American Spinal Injury Association Impairment Scale (ASIA) is a standardized neurological examination to assess the sensory and motor levels which were affected by the spinal cord injury. The scale has five classification levels, ranging from A (complete loss of neural function in the affected area) to E (completely normal).

Table 9: Summary statistics for outcomes related to hospital stay and survival at discharge

		MM	TI	Treatment difference (MM-TI)	Unadjusted treatment effect (OR/HR/mean difference (95% CI))	Adjusted treatment effect (OR/HR/mean difference (95% CI))
Receive any higher-level care, No. (%)	**Yes - Level 3 (ICU/ITU)**					
	Yes - Level 2 (HDU)					
	No					

	Missing					
Length of critical care unit stay (days)* (all patients admitted to critical care unit)	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
Length of critical care unit stay (days)* (patients alive at critical care unit discharge)	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
Length of hospital stay (days)* (all patients)	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
Length of hospital stay (days)* (patients alive at hospital discharge)	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
Hospital discharge destination, No. (%)	Home					
	Community based support/care					
	Another hospital					
	Other					
	Deceased in hospital					
	Missing					

*Note: *, analysed as continuous and time to event outcomes.*

Table 10: Survival at days 30, 90, 180

		MM	TI	Treatment difference (MM- TI)	Unadjusted treatment effect (OR (95% CI))	Adjusted treatment effect (OR (95% CI))
Survival at 30 days, No. (%)	Alive					
	Deceased					
	Missing					
	- Unobtainable					
	- Withdrawal					
Survival at 90 days, No. (%)	Alive					
	Deceased					
	Missing					
	- Unobtainable					
	- Withdrawal					
Survival at 180 days, No. (%)	Alive					
	Deceased					
	Missing					
	- Unobtainable					
	- Withdrawal					

Table 11: Pre-hospital analgesia

		MM	TI	Treatment difference (MM- TI)	Unadjusted treatment effect (OR (95% CI))	Adjusted treatment effect (OR (95% CI))
Pre-hospital analgesia, No. (%)	None					
	Paracetamol					
	Codeine					
	Morphine					
	Penthrox					
	Ketamine					
	Fentanyl					

	Other					
	Missing					

Table 12: Other interventions for c-spine injury in the first 30 days or hospital discharge

		MM	TI	Treatment difference (MM- TI)	Unadjusted treatment effect (OR (95% CI))	Adjusted treatment effect (OR (95% CI))
Further interventions for c-spine injury in the first 30 days or hospital discharge, No. (%)	None					
	Immobilisation					
	Immobilisation - soft collar					
	Immobilisation - hard collar					
	Immobilisation - traction					
	Immobilisation - halo					
	Immobilisation - other					
	Surgery					
	Surgery - anterior fixation					
	Surgery - posterior fixation					
	Surgery - anterior and posterior fixation					
	Surgery - other					
	Missing					

Table 13: Summary of health-related quality of life at hospital discharge, days 30 and 180

		MM	TI	Treatment difference (MM- TI)	Unadjusted treatment effect (mean difference (95% CI))	Adjusted treatment effect (mean difference (95% CI))
EQ-5D-5L index score at hospital discharge	N					
	Mean (SD)					
	Median (IQR)					

	Range					
	Missing					
	- Unobtainable					
	- Withdrawn					
EQ-5D-5L Visual Analogue Scale score at hospital discharge	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawn					
EQ-5D-5L index score at 30 days	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawn					
EQ-5D-5L Visual Analogue Scale score at 30 days	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawn					
EQ-5D-5L index score at 180 days	N					
	Mean (SD)					
	Median (IQR)					
	Range					

	Missing					
	- Unobtainable					
	- Withdrawn					
EQ-5D-5L Visual Analogue Scale score at 180 days	N					
	Mean (SD)					
	Median (IQR)					
	Range					
	Missing					
	- Unobtainable					
	- Withdrawn					

8.5 Safety Outcomes

Table 14: Detailed adverse events by treatment arm and total

			MM	TI	Total/p value
Adverse event (AE)	Pressure sore	Total patients with at least one AE			
		Incidence rate (per 100 patients)			
	Aspiration pneumonia	Total patients with at least one AE			
		Incidence rate (per 100 patients)			
	Intracranial hypertension	Total patients with at least one AE			
		Incidence rate (per 100 patients)			
Total AE		Total patients with at least one AE			
		Incidence rate (per 100 patients)			

Table 15: Detailed serious adverse events by treatment arm and total

	Details of serious adverse events			
		MM	TI	Total/p value
SAE	N			
	Incidence rate (per 100 patients)			
SAE (Movement Minimisation)				
	Details			
No.1				
No.2				
…				
SAE (Triple Immobilisation)				
	Details			
No.1				
No.2				
…				

Table 16: Causality of serious adverse events by treatment arm and total

Causality	SAEs		
	MM	TI	Total
Definitely			
Probably			
Possibly			
Unlikely			
Unrelated			

Table 17: Non-compliance by treatment arm and overall (excluding treatment non-compliance)

		MM	TI	Total
Type of non-compliance, No. (%)	Deviation			
	Violation			
	Serious Breach			
	Data Breach			
	Processor Data Breach			
Category of non-compliance, No. (%)	Consent			
	Eligibility & Randomisation			
	Data collection			
	Document Design and Management			
	Contracts and approvals			
	Safety Reporting			
	Set-up, Resource and Feasibility			
	Staff delegation and oversight			

	Transparency			
	External communications			
	Staff Safety			
	Trial Closure			
	Other			

Table 18: Unblinding by treatment arm and overall

		MM	TI	Total
Unblinding, No. (%)	Yes			
	No			

8.6 Sensitivity analysis

Table 19: Summary of sensitivity analysis

Method	FIM-Motor score at hospital discharge	MM	TI	Unadjusted treatment effect (Mean difference (95% CI))	Adjusted treatment effect (Mean difference (95% CI))
Median imputation method	N				
	Mean (SD)				
	Median (IQR)				
	Range				
	Missing				
	Unobtainable				
	Withdrawal				
Multiple imputation by chained equations (MICE)	N				
	Mean (SD)				
	Median (IQR)				
	Range				
	Missing				
	- Unobtainable				
	- Withdrawal				

Tipping point analysis	N				
	Mean (SD)				
	Median (IQR)				
	Range				
	Missing				
	- Unobtainable				
	- Withdrawal				
Inverse Probability Weighting (IPW)	N				
	Mean (SD)				
	Median (IQR)				
	Range				
	Missing				
	- Unobtainable				
	- Withdrawal				

8.7 Subgroup analysis

Table 20: Summary of subgroup analysis

Subgroups		FIM-Motor score at hospital discharge	MM	TI	Unadjusted effect estimate (95% CI)	Adjusted effect estimate (95% CI)	Unadjusted interaction effect (95% CI)	Adjusted interaction effect (95% CI)
Age group	Age < 65	N						
		Mean (SD)						
		Median (IQR)						
		Range						
		Missing						
		- Unobtainable						
		- Withdrawal						
	Age ≥ 65	N						

		Mean (SD)						
		Median (IQR)						
		Range						
		Missing						
		- Unobtainable						
		- Withdrawal						
Mechanism of injury	Fall<2m	N						
		Mean (SD)						
		Median (IQR)						
		Range						
		Missing						
		- Unobtainable						
		- Withdrawal						
	Other mechanisms	N						
		Mean (SD)						
		Median (IQR)						
		Range						
		Missing						
		- Unobtainable						
		- Withdrawal						
Spinal pain/discomfort	0-3 (mild pain)	N						
		Mean (SD)						
		Median (IQR)						
		Range						
		Missing						
		- Unobtainable						
		- Withdrawal						
	4-6 (mild pain)	N						
		Mean (SD)						
		Median (IQR)						

		Range						
		Missing						
		- Unobtainable						
		- Withdrawal						
	7-10 (severe pain)	N						
		Mean (SD)						
		Median (IQR)						
		Range						
		Missing						
		- Unobtainable						
		- Withdrawal						