**PROTOCOL**

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

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# SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

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

**For and on behalf of the Trial Sponsor:**

Signature: ..... .....

Date (dd/mmm/yy)

Name (please print): .....

Position: .....

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Date (dd/mmm/yy)

Name: (please print): .....

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## TRIAL SUMMARY

| | | |
|---|---|---|
| **Trial Title** | Randomised controlled trial of the clinical and cost-effectiveness of cervical spine immobilisation following blunt trauma (SIS trial) | |
| **Internal ref. number (or short title)** | SIS trial | |
| **Trial Design** | A multi-centre, open-label, pragmatic, pre-hospital, non-inferiority randomised controlled trial with health economic evaluation to determine the effectiveness of immobilisation regimes involving movement minimisation and triple immobilisation (current NHS practice) in patients with cervical spine (c-spine) injury recruited in a pre-hospital setting. | |
| **Trial Participants** | Patients (any age) in a pre-hospital setting with potential or suspected c-spine injury. | |
| **Planned sample size** | 2010 participants | |
| **Treatment Duration** | The interventions will be administered at initial pre-hospital clinical assessment and will remain in place for as long as is clinically required. | |
| **Follow-up Duration** | Participants will be followed-up for 180 days | |
| **Planned Trial Period** | 01 November 2022 – 30 April 2026 with an internal pilot phase 01 November 2022 – 31 Aug 2024 | |
| | **Objectives** | **Outcome Measures** |
| **Primary** | To determine whether movement minimisation is deemed non-inferior compared to triple immobilisation in relation to functional outcome at hospital discharge. | Functional Independence Measure (Motor) score |
| **Secondary** | To determine the effects of immobilisation techniques on clinical, patient-centred and economic outcomes pre-hospital, in hospital and at 180 days post-randomisation. | Need for pre-hospital analgesia<br>Neurological change (randomisation to hospital discharge)<br>Mortality (30, 90 and 180 days) Length of stay in critical care and hospital<br>Further intervention for c-spine injury<br>Costs and resource utilisation Adverse events |
| **Quality of Life** | To determine the effects of immobilisation techniques on patient-centred outcomes pre-hospital, in hospital and at 180 days post-randomisation. | Quality of life measurements (EQ-5D-5L/EQ-5D-Y) |

## LIST OF ABBREVIATIONS/GLOSSARY

| Abbreviation | Explanation |
|---|---|
| AE | Adverse Event |
| ASIA | American Spinal Injury Association Impairment Scale |
| CI | Chief Investigator |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| C-spine | Cervical spine |
| CTU | Clinical Trials Unit |
| DMC | Data Monitoring Committee |
| EQ-5D-5L | EuroQol five-domain health utility measure (five level) |
| EQ-5D-Y | EuroQol five-domain health utility measure (Youth) |
| FIM | Functional Independence Measurement |
| GCP | Good Clinical Practice |
| ICF | Informed Consent Form |
| IRAS | Integrated Research Application System |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| MRC | Medical Research Council |
| NIHR | The National Institute for Health Research |
| NMTR | National Major Trauma Registry |
| PI | Principal Investigator |
| PPI | Patient & Public Involvement |
| QoL | Quality of Life |
| RCT | Randomised Controlled Trial |
| REC | Research Ethics Committee |
| R&D | Research and Development |
| SAE | Serious Adverse Event |
| ScHARR | School of Health and Related Research |
| SOP | Standard Operating Procedure |
| TARN | Trauma Audit & Research Network |
| TSC | Trial Steering Committee |
| VOI | Value of Information |
| WCTU | Warwick Clinical Trials Unit |

# 1. BACKGROUND

## 1.1 Existing knowledge

NHS Ambulances use cervical collars for spinal immobilisation in large numbers of "at risk" injured patients (~ 80,000/year in UK, 5 million/ year in USA[1]) but the numbers of patients shown to have a significant cervical vertebrae or spinal cord injury (SCI) is much less; 5476 in 2017 (from National Major Trauma Registry (NMTR), formerly known as the Trauma Audit & Research Network- TARN) with just under one third having cervical SCI (n=1376). A large number of patients are immobilised due to the challenges, even using the NICE decision rule, to confidently rule out unstable cervical spine (c-spine) fractures. Most civilian trauma is "blunt" (falls and road traffic collisions), where precise injury assessment is not possible in unconscious patients and difficult in conscious patients, who may have whiplash muscle injury, and may initially appear similar to a patient with an unstable spinal fracture. This means that at least 75% of patients exposed to the discomfort and complications of spinal immobilisation have no potential benefit. In the majority of immobilised patients, injuries to the spine are ruled out by assessment or imaging in the emergency department (ED) which allows removal of immobilisation within hours; however, ruling out an unstable spinal fracture may take much longer in comatose patients with brain injuries. Previous reports suggested that after imaging, 2-4% of major trauma patients have a significant c-spine injury. A published study using NMTR data from 1998-2009 shows 2.3% of major trauma patients had a significant c-spine fracture or dislocation and 0.8% had a cervical SCI diagnosed prior to hospital discharge[2]. The expansion of NMTR to all trauma-receiving hospitals and better access to imaging has seen the average age of major trauma patients increase considerably in the intervening decade (current NMTR median age = 59 years). The most recent analysis in 2017 suggests the true prevalence of significant potentially unstable c-spine injury and SCI within major trauma patients is therefore more than double (6% & 1.8% respectively). In the older population, cord contusion without fracture (e.g. central cord syndrome) is also more common. Recruitment will occur across the UK ensuring areas with a high disease burden make a substantive contribution.

## 1.2 Hypothesis

The primary hypothesis is that movement minimisation (intervention) is deemed non-inferior (i.e., no worse) compared to triple mobilisation (control) in patients with potential c-spine injury (pre-imaging) following blunt trauma, in relation to motor function at hospital discharge following randomisation.

## 1.3 Need for a trial

Spinal Immobilisation has been an essential standard of potential spinal injury care for 20 years[3]. However, gold standard "Triple Immobilisation" can be associated with neurological harm (for example if used in patients who unknowingly have ankylosing spondylitis)[4,5]. The natural history following spinal cord injury (SCI) is that it often worsens as cord contusion progresses and this may mistakenly be attributed to lack of immobilisation. Hence the costs of not understanding SCI and immobilisation include not just the cost of collars (in UK ~ £500,000 year), but the cost of health complications and associated medico-legal costs, which can be considerable[6]. There is a significant body of opinion questioning the benefits of cervical immobilisation[7,8]. Several ambulance services in Scandinavia and Australia have reduced the use of cervical collars, without an overt increase in complications. This is known as movement minimisation. Movement minimisation uses 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 an ambulance stretcher. However, robust evidence is

needed to know if movement minimisation is non-inferior than triple immobilisation before adopting across the NHS given the substantial personal, healthcare and medico-legal consequences of SCI[9]. It is vital that a well-structured trial resolves this issue.

A survey of 614 health care professionals (373 Pre-Hospital Care, 154 Emergency Medicine, 34 Neurosurgery, 11 ITU, 11 Care of Elderly and 11 Anaesthetics) has demonstrated that 80% feel that current c-spine immobilisation guidelines are not appropriate. The majority (81.4%) were happy to randomise patients with potential spinal injury to either triple immobilisation or movement minimisation techniques with 64.4% thinking this should not be restricted to a specific conscious level. Respondents prioritised incidence of neurological deficit (58.6%) and a functional outcome measure (49.9%) as primary outcome measures. This proposal describes a definitive randomised trial to determine the clinical and cost effectiveness immobilisation regimes for spinal cord injury.

This clinician survey, patient & public views and the pragmatic requirements of undertaking a trial informed the decision to use a functional outcome measure as the primary end-point, supported by important clinical (neurological deterioration, mortality, morbidity, adverse events, resource use) secondary end-points and health economic analysis. The trial will efficiently utilise the NMTR data to support measurement of clinical & cost effectiveness. The trial will provide the definitive answer to whether it is appropriate to use movement minimisation compared to triple immobilisation, in patients with potential c-spine injury.

## 1.4 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation (e.g., Mental Capacity Act 2005 (England and Wales) and Mental Capacity Act (Northern Ireland) 2016) and Warwick Standard Operating Procedures (SOPs). This has been agreed with the Sponsor. All data will be stored securely and held in accordance with UK GDPR.

This is a trial conducted in patients experiencing sudden and unexpected trauma and therefore there are ethical considerations in recruiting patients in this setting. Due to the emergency and distressing nature of the injuries, most potential participants will not have capacity for fully informed consent. In addition, it would be dangerous and inappropriate to delay treatment to consult with a designated family member/consultee. As a result, emergency waiver of consent will be used in SIS. Consent will be obtained in line with the legal requirements for obtaining consent in patients without capacity in England and Wales (Mental Capacity Act 2005)[10] and Northern Ireland (Mental Capacity Act (NI) 2016. Due to the need for deferred consent, prior to consent being obtained only non-identifiable data will be made available to the trial team.

## 1.5 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement[11].

Up-to-date information on CONSORT revisions, downloadable check lists and flow chart are available on the CONSORT web site: *http://www.consort-statement.org/*

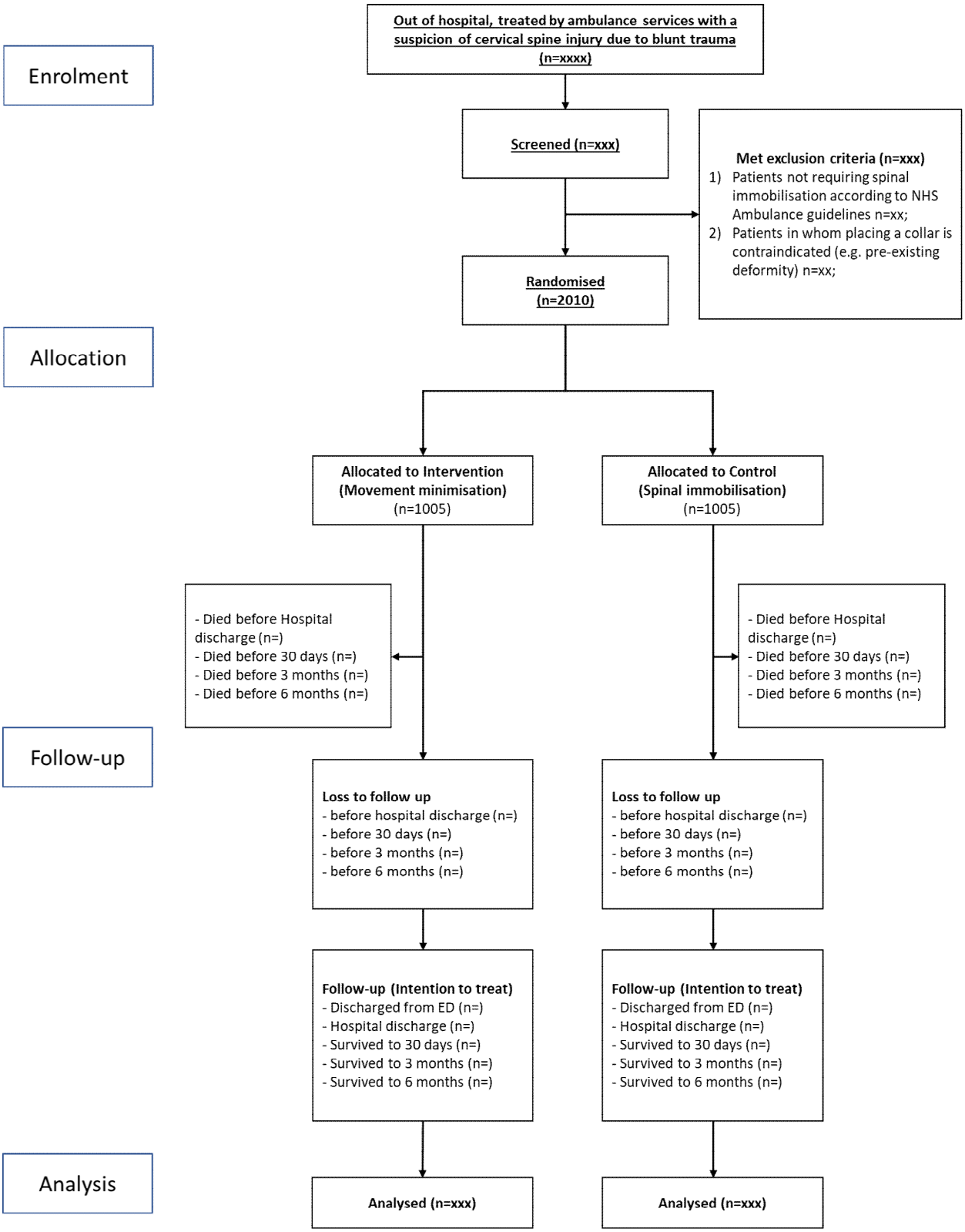
# 2. TRIAL DESIGN

## 2.1 Trial summary and flow diagram

This is a UK-wide, open-label, pragmatic, phase 3, multi-centre, individually randomised, controlled, non-inferiority, clinical and cost-effectiveness trial, with blinded assessment of outcome during hospital stay and at 180 days. The trial design is described in PICO terms below and in Figure 1.

**Population:** Patients (all ages) in a pre-hospital setting with potential or suspected c-spine injury
**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)
**Outcomes:** Clinical and cost effectiveness from randomisation, up to and including hospital discharge and at 6 months; longer term cost-effectiveness model
The main trial will be preceded by a 4-site pilot phase which will be accompanied by a value of information (VOI) analysis. This analysis will assess the feasibility and value for money of the proposed large-scale clinical trial.

**Figure 1** **Trial flow diagram**



## 2.2 Aims and objectives

### 2.2.1 Primary objective

To determine whether movement minimisation is deemed non-inferior compared to triple immobilisation in relation to functional outcome (as assessed by the Functional Independence Measure 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 utilisation (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.

## 2.3 Outcome measures

**FIM:** The primary outcome for the trial is the Functional Independence Measurement (motor) (FIM-motor). The FIM was developed as a functional assessment measure for all diagnoses in the rehabilitation setting and has been used to assess outcome in trauma populations away from the rehabilitation setting[12]. The FIM consists of 18 items across 6 domains: self-care; sphincter control; mobility; locomotion; communication; and social cognition. There are 13 items related to motor activities and 5 assessing cognitive function. 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. Performance on each item is summed to form the FIM total score, which ranges from 18 (lowest function) to 126 (highest function). There are 2 additional sub-scores. The FIM cognitive score uses the 5 cognitive items to create a score from 5 (lowest cognitive function) to 35 (highest cognitive function). The 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). The FIM motor score at discharge has also been found to be a significant independent predictor of return to work or study[12]. Moreover, FIM motor reflects well the functional status of individuals following traumatic spinal cord injury[13].

**ASIA Impairment Scale[14]:** The American Spinal Injury Association Impairment Scale (ASIA) is a standardized neurological examination used by the rehabilitation team to assess the sensory and

motor levels which were affected by the spinal cord injury. The scale has five classification levels, ranging from complete loss of neural function in the affected area to completely normal. Neurological deterioration is defined as the change from 'E' – normal to 'A-D' – impairment.

**EQ-5D-5L[15]:** The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions.

The EQ-5D-Y[15]: (Used for youth patients). The descriptive system comprises the following five dimensions: mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy. Each dimension has 3 levels: no problems, some problems and a lot of problems. The younger patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions.

### 2.3.1 Effectiveness

Primary effectiveness outcome:

- Total Functional Independence Measurement motor (FIM-motor) score at discharge. The FIM is an 18-item instrument measuring a person's level of disability in terms of burden of care. The FIM should be rated by the consensus opinion of a multidisciplinary team, but the evaluation is often performed by a single professional.

Secondary effectiveness outcomes:

- FIM-motor at 30 days, 180 days after randomisation at video clinic or follow up appointment;
- FIM-total and cognition scales at discharge, 30 days and 180-day at video clinic or follow up appointment;
- ASIA Impairment Scale at discharge;
- Mortality (at days 30, 90 and 180);
- 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).

### 2.3.2 Safety

- Adverse events: pressure sores, aspiration pneumonia, intracranial hypertension.

### 2.3.3 Others

- Primary Health Care System benefit measure:
    - Assessment of in-trial cost effectiveness
- Secondary Health Care System benefit measures:
    - 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.

## 2.4 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

### 2.4.1 Inclusion criteria

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

### 2.4.2 Exclusion criteria

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

## 2.5 Participant identification / Screening

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 inclusion criteria for the trial but not entered into the trial along with the reasons for non-enrolment. Recording this information is required to establish an unbiased study population and for reporting according to the CONSORT statement[16,17].

## 2.6 Site Staff Training

Ambulance staff on scene will identify potential participants and where appropriate (i.e. potential participant is conscious) ascertain that the participant is willing to be enrolled into the trial. A programme of training will be provided to ambulance service staff responsible for delivering the trial for their service. This will include the following: trial background; randomisation procedures; core principles of Good Clinical Practice; inclusion and exclusion criteria; data collection and documentation; and ethical issues and consent.

This will be delivered in person, via video or teleconference or via web-based training resources
Training records will be maintained by ambulance services.

## 2.7 Informed consent

The majority of patients who have suffered a traumatic injury will lack capacity and/or will be minors. Due to the sudden, unexpected and emergency nature of trauma it is impractical to seek informed consent from a person with parental responsibility (in the case of minors) or a consultee for incapacitated adults before randomisation into the trial.

It is expected that the majority of participants will lack capacity throughout the recruitment and the intervention and even though an occasional participant may retain capacity, their clinical condition will require immediate treatment. Therefore, it would be inappropriate to attempt to gain informed consent at this time, as it could delay life-saving treatment. It would also be clinically unjustifiable to delay treatment in order to obtain full informed consent from a consultee or parent/guardian. Then even if such a consultee or person with parental responsibility were immediately available, the emotional distress of the situation would make it difficult to obtain an informed decision in the minimal time available. Furthermore, a sudden traumatic injury cannot be predicted or foreseen, and as such there is no opportunity to seek consent in advance. As a result, SIS cannot be conducted on the basis of prospective informed consent. Participants without capacity will be enrolled in such trials as SIS without prior advice from a consultee if:

- Treatment needs to be given urgently;
- It is not reasonably practicable to seek advice from a consultee;
- The procedure is approved by a NHS Research Ethics Committee; and
- A consultee is consulted as soon as possible to seek advice on the participant's likely views and feelings.

Common law also enables research involving children and young people in emergency situations such as trauma if:

- The procedure is approved by a NHS Research Ethics Committee
- You cannot address the same research question by recruiting from a non-emergency environment, and
- Your research is of potential benefit to the child / young person themselves, and
- Someone with parental responsibility for the child / young person is informed about the research as soon as possible, and
- Consent (and assent) is sought as soon as possible, and
- You make clear to the child / young person or their parent (if the child / young person is not competent) that the child / young person can withdraw (or be withdrawn by their parent) at any time without penalty.

As the SIS trial fulfils the above criteria and carries minimal risk (there are no additional risks as both methods of spinal immobilisation are already used as normal practice in the UK), participants will be enrolled under the deferred consent model. Patients or their legal guardian (for children) or consultee (for adults lacking capacity) will be approached regarding trial participation as soon as it is appropriate to do so. Upon arrival at the scene, should the potential participant be conscious, attending ambulance staff will make every effort to verbally ascertain whether they are happy to be recruited

into SIS. However, obtaining formal consent will take place after hospital transfer and when it is appropriate to do so. Outside of the clinical care team, only non-identifiable data will be collected prior to consent.

### 2.7.1 Opt out consent for patients lost at discharge

During the pilot phase of the study, it became clear that due to the nature of their condition many patients are admitted late in an evening, have their c-spine cleared and are discharged before they can be consented (sometimes on the same day as admission). This has made it difficult for site staff to get consent from these patients for trial participation even with pre-existing measures in place (x3 telephone call consent as detailed below).

We will adopt an opt-out strategy for any patients assented onto the trial at randomisation, but who have been lost following discharge (sites unable to consent). The study will continue in the same way as the pilot, with verbal agreement (assent) at the time of randomisation in the pre-hospital phase by paramedics. In hospital site staff must attempt to gain consent in person as usual and try to get telephone consent when this has not occurred.

The trial intervention will have been completed at the point of approach, and some non-identifiable data collected on the WCTU trial database. For any patients discharged on the same day and/or not contactable by trial staff members (i.e. post 3 calls attempt) to explain the study, the PIS will be sent via post or email with an opt out consent form attached. Patients can fill in the opt out form and use this to contact the trial team about their decision to opt out, post discharge. This will also be recorded in the notes. If no opt out request is received, we will assume consent for the period of hospitalisation and the data from this (e.g. that their c-spine was cleared, and they returned home neurologically the same i.e. the FIM score was unchanged) will be included in the study. At each subsequent follow up timepoint post discharge (30, 90 and 180 days) where survival and PROMs data is collected site staff will continue to attempt to contact the patient to collect these, if contact is successful they will remind the participant of their right to opt out at each timepoint.

This protocol has been prepared for recruitment in England, Wales and Northern Ireland, in consideration of the legal requirements in these nations.

### 2.7.2 Consent for adult participants after enrolment

This section is relevant to participants aged ≥ 16 years, as common law presumes that young people aged between 16 and 18 are usually competent to give consent to treatment.

If the participant regains mental capacity a researcher in hospital will approach them at an appropriate time, to discuss ongoing trial participation. The trial intervention will have been completed at the point of approach, and some non-identifiable data collected on the WCTU trial database. The approach may be made in-person, by telephone, or via videoconferencing depending on participant preference, local policy, and equipment availability. The researcher will inform the participant (or their consultee) of their enrolment and explain that the focus of the consent process relates to ongoing participation, including the collection of patient reported outcome measures

through questionnaires and data collection from medical records. The researcher will provide verbal information about the trial and the participant information sheet. The participant will be given adequate time to review the information sheet and given the opportunity to ask questions. The participant's consent will be recorded on a signed consent form, counter-signed by the researcher. The consent form may be signed physically or digitally (where this option is available). Due to the injuries sustained or risk of infection transmission, some participants may only be able to provide verbal consent. Where the participant is unable to sign the form either in wet ink or electronically, the PIS will be provided by a member of staff, and all clauses on the consent form will be discussed, in the presence of a witness. Consent to these clauses will be recorded on the consent form, signed by the staff member obtaining consent and the witness present.

Where the participant is taken to a non-participating hospital the participant will be approached for consent by a member of the trial or ambulance service research team, using the same process as above.

### 2.7.3 Consent for adult participants who lack capacity after enrolment

Participants may lack capacity following a traumatic event.

If the participant lacks capacity to make a decision about ongoing trial participation, a member of the research team will approach a personal consultee who meets the criteria described in the Mental Capacity Act 2005 (someone who is engaged in caring for the participant (not professionally or for payment) or is interested in his/her welfare, and is prepared to be consulted). The researcher will provide information about the trial and the participant information sheet and a cover note. The consultee will be given adequate time to review the information sheet and an opportunity to ask questions. The consultee will be asked to consider what decision the participant is likely to have made if they had mental capacity. If no personal consultee is available, or a potential personal consultee is unwilling to take on this role, researchers will approach a professional consultee who is not connected in any way with the conduct of the trial. The same process, as described for the personal consultee, will be followed.

The consultee may decide it is not an appropriate time to discuss the trial or they may decide that the participant would not want to take part in which case their feelings will be respected and their decision about taking part will be recorded.

If an initial approach is made to a professional consultee and a personal consultee subsequently becomes available, then the opinion of the personal consultee will be sought. This will override any decision made by the professional consultee.

The consultee's agreement to the collection of routine health data and patient reported outcome measures (which will include completing questionnaires on behalf of the participant) will be recorded on a signed declaration form, counter-signed by the researcher. This form may be signed physically or digitally (where this option is available). Where the participant is unable to sign the form either in wet ink or electronically, the PIS will be provided by a member of staff, and all clauses on the consent form will be discussed, in the presence of a witness. Consent to these clauses will be recorded on the consent form, signed by the staff member obtaining consent and the witness present.

If an initial approach is made to a personal or professional consultee and the participant subsequently regains capacity prior to hospital discharge, then the participant's consent will be sought. This will override any opinion given by the personal or professional consultee.

For England and Wales: If a participant who has previously given their consent to continue in the trial loses capacity, we will approach a consultee for consent to complete the questionnaires on their behalf using same approach outlined above. If the participant regains capacity subsequently, we will seek their consent to continue in the trial and proceed according to their wishes.

For Northern Ireland: If a participant who has previously given their consent to continue in the trial loses capacity, we will continue with data collection under the terms of their original consent, as per the Mental Capacity Act (NI) 2016.

Where the participant is taken to a non-participating hospital the consultee will be approached for consent by a member of the trial or ambulance service research team, using the same process as above.

### 2.7.4 Consent arrangements for participants under the age of 16

There is no statue in England, Wales or Northern Ireland governing a child's right to consent to take part in non-CTIMP trials. As such, it is commonly assumed that the principle of 'Gillick competent' can be applied to the conduct of research.

A child/young person's right to provide consent depends on their capacity to understand the research, and is influenced by how the presentation of information and the language used. Therefore, a Young Person's separate information sheet has been developed for use in the trial.

If a participant under 16 years is deemed to be "Gillick competent" to provide consent as soon as practical and appropriate to do so the researcher will approach the participant regarding trial participant. The researcher will provide information about the trial and the Young Person's Information Sheet. The participant will be given adequate time to review the information sheet and an opportunity to ask questions. If the participant agrees to continued participation, they will be asked to sign a patient consent form. The consent form may be signed physically or where this option is available, digitally. Where the participant is unable to sign the form either in wet ink or electronically, the PIS will be provided by a member of staff, and all clauses on the consent form will be discussed, in the presence of a witness. Consent to these clauses will be recorded on the consent form, signed by the staff member obtaining consent and the witness present. When a young person is believed to be competent, consent from those with parental responsibility it is not legally necessary. But, where possible, researchers may wish to involve parents in the decision making as this is often encouraged.

Where the child or young person is not competent, consent should be sought from an appropriate adult such as a parent or legal guardian as soon as practical and appropriate to do so. They will be given adequate time to review the parent or legal guardian information sheet and an opportunity to

ask questions. If they agree for the participant to continue to take part in this trial, they will be asked to sign the parent and guardian consent form. The consent form may be signed physically or where this option is available, digitally. Where the parent or guardian is unable to sign the form either in wet ink or electronically, the PIS will be provided by a member of staff, and all clauses on the consent form will be discussed, in the presence of a witness. Consent to these clauses will be recorded on the consent form, signed by the staff member obtaining consent and the witness present.

Even when a child or young person is deemed not competent to make a decision regarding ongoing trial participation, it is important that where practical and appropriate the participant wishes are sought and considered.

### 2.7.5 Approaching patients or their consultee following discharge

In rare circumstances, participant (or appropriate adult for children/young people who lack competence) consent or a personal/professional consultee opinion may not be obtained before hospital discharge.

If this occurs, the hospital or ambulance (if taken to a non-participating hospital) research team will contact the participant (or appropriate adult for children/young people who lack competence) or their consultee (if it is known that the participant lacks mental capacity) to seek consent or an opinion. Up to 3 contact attempts will be made on different days and times, prior to the day 30 follow up visit. The researcher will use available systems to determine correct contact information and, where appropriate, to ensure the participant is still alive. Where available, more than one system will be accessed to determine survival status.

If the participant (or appropriate adult for children/young people who lack competence) or their consultee does not respond, non-identifiable data which have already been collected will be retained, and no further data collection will continue.

### 2.7.6 Patients who do not survive

In comparison to other emergency care trials, survival rates are expected to be high in this study. However, we need to account for the situation in which the participant unfortunately does not survive prior to the point of consent.

At the point of death, the trial intervention will have been completed and no further active follow-up will occur. The purpose of any communication with the participant's loved ones would be to inform them about trial involvement. On the one hand, providing information about trial participation ensures openness and transparency about trial recruitment, and it reduces the likelihood of family members inadvertently finding out about trial participation at a later date. On the other hand, knowledge about trial participation may place additional emotional burden on the participant's loved one at a time of already heightened emotional distress due to the loss of their relative or friend.

To address this, we will adopt the strategy used which is often used in emergency care studies, which aims to carefully balance the need for transparency with the need to minimise the distress of the participant's loved ones. As such, we will adopt a strategy of providing passive information, whereby trial information is made publicly available (e.g., trial websites). This approach enables individuals to make a choice about whether they wish to seek further information and the timing of that approach. A key disadvantage is uncertainty as to whether the loved ones of all participants will see this information. This approach, however, has been widely used across previous UK emergency care research.

We have discussed this in detail with patient representatives who support this approach.

## 2.8 Randomisation

### 2.8.1 Randomisation

Patients will be randomised on scene by the recruiting paramedic/ambulance service practitioner. 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 such as 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.

### 2.8.2 Post-randomisation withdrawals, exclusions and moves out of region

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. In the event that 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.

## 2.9 Trial treatments / intervention

### 2.9.1 Trial treatment(s) / intervention

- **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:** Cervical collar, head blocks and tape (as per NICE guidelines, https://www.nice.org.uk/guidance/ng41/chapter/recommendations).

### 2.9.2 Compliance/contamination

- It is not anticipated compliance will be an issue in the trial, but compliance will be monitored closely via data entry, with monthly oversight provided by the Trial Management Group

## 2.10 Blinding

### 2.10.1 Methods for ensuring 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.

### 2.10.2 Methods for unblinding the trial

There is no requirement for unblinding as the trial is open-label.

## 2.11 Co-enrolment into other trials

Co-enrolment with other trials will be reviewed on a case-by-case basis in accordance with the national NIHR-supported co-enrolment guidelines.

## 2.12 Pilot phase

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, and will aim to recruit 624 patients. In particular, we will audit: (a) screening data; (b) recruitment; (c) reasons for exclusion; (d) protocol adherence, crossovers and fidelity to the intervention; (e) implementation of the training and protocol into practice, using screening logs, case report forms (CRFs) and virtual site visits.

Due to delays in trial set up the NIHR allowed the study to progress beyond their pilot in order to demonstrate feasibility.

Trial progression criteria will be:

| | Red | Amber | Green |
|---|---|---|---|
| **RECRUITMENT** | | | |
| % Threshold | <30% | 30-74% | 75-100% |
| **Total number of participants recruited** | <187 | 187 - 467 | 468 - 624 |

Success criteria for recruitment will be
(a) 75-100% recruitment: progress to main trial following a review of screening logs and protocol. Any barriers for recruitment will be addressed;
(b) 30-74% recruitment: progress to main trial with additional sites being recruited as well as a screening log and protocol review;
(c) less than 30% recruitment: the decision to progress will be made by the Trial Steering Committee in association with the HTA secretariat.

On reaching the pre-defined success criteria, the internal pilot will run seamlessly into the main trial. The pilot study results will be reported in accordance with the CONSORT guideline for pilot studies[18].

### 2.13 End of trial

The trial will end when the last participant recruited into the trial has completed their 6-month follow-up, or on receipt of the final routinely collected dataset whichever is later.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases

The Research Ethics Committee will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

## 3. METHODS AND ASSESSMENTS

### 3.1 Schedule of delivery of intervention and data collection

Table 1 describes the trial assessments and timepoints for data collection.

**Table 1 Trial assessments**

| Visit | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| **Visit Window** (No. Weeks ± No. Days) | **Baseline** | **Hospital stay** | **At discharge** | **30 days (± 14 days)** | **90 days (± 28 days)** | **180 days (± 28 days)** |
| Informed consent | ✓* | ✓* | | | | |
| Medical history | ✓ | | | | | |
| Inclusion/exclusion criteria | ✓ | | | | | |
| Intervention | ✓ | | | | | |
| FIM (motor and cognition) | | ✓ | ✓ | ✓ | | ✓ |
| ASIA neurological scale | | ✓ | ✓ | | | |
| Intercranial hypertension | | ✓ | | | | |
| Length of stay | | | ✓ | | | |
| Further treatment for c-spine injury | | | ✓ | ✓ | | |
| Cost and resource utilisation | | | ✓ | ✓ | | ✓ |
| Quality of Life (EQ-5D-5L/EQ-5D-Y) | | ✓ | ✓ | ✓ | | ✓ |
| Adverse events | ✓ | ✓ | ✓ | | | |
| Survival status | | | | ✓ | ✓ | ✓ |

*Due to the emergency nature of the trial, participants will be enrolled in the trial prior to consent. Once participants have recovered sufficiently (usually around the time of discharge from the Intensive Care Unit) and whilst they are still in hospital, a member of the hospital research team will approach the patient (or if they lack capacity a consultee) to explain the trial and seek consent to continue in the trial

## 3.2 Data Collection

### 3.2.1 Participant enrolment

The randomisation PWA will collect the following identifiable data e.g.

- Date/time of injury
- Date/time received in hospital
- Initials
- Hospital/NHS number
- CAD/EPR number
- Neurological impairment
- Analgesia given (pre-hospital)

7.2.2 Baseline

The following data will be collected at the time of hospital admission by the ambulance service/hospital research team;

- Gender
- Age
- Neurological impairment
- Duration of immobilisation (up until arrival at hospital)
- Mechanism of injury (e.g. road traffic accident/push bike/fall/sports injury/assault)

### 3.2.2 In hospital

The following data will be collected in hospital. These data will include:

- Duration of immobilisation in hospital
- Analgesia given (in hospital)
- CT scan appearance
- Details of cervical spine injury
- Mortality
- Evidence of infection
- The length of ICU stay and level of stay
- The length of hospital stay (dates)
- Interventions used for c-spine injury in the hospital and up to discharge
- Discharge destination
- Adverse events (e.g. chest infections, pressure sores, raised ICP)
- Other injuries sustained (randomisation to discharge)
- Injury Severity Score

The following will be collected as close as possible to the point of admission and discharge

- FIM (total and sub-scales)
- ASIA neurological scale
- Variables that will assist in the health economics analysis (including EQ-5D-5L/EQ-5D-Y).

If participants are discharged from the emergency department before a member of the local research team has had the opportunity to collect this data, their FIM-motor score will be recorded as 7 (score for total independence).

### 3.2.3 Follow-up

Survival status will be collected by hospital research staff for all participants up to 180 days.

For patients who have been discharged, a tele-video clinic or out-patient follow-up visit will be arranged at 6 months after randomisation by a member of the research team from Imperial College London, where the FIM score will be documented, along with the other relevant data. If the patient is still in hospital, hospital research staff will aim to obtain their data by visiting them and if required, assisting them with the completion of this questionnaire.

# 4. ADVERSE EVENT MANAGEMENT

## 4.1 Definitions

| | |
|---|---|
| **Adverse Event (AE)** | An Adverse Event is defined as any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with the administration of the IMP. |
| **Serious Adverse Event (SAE)** | A Serious Adverse Event is an AE that fulfils one or more of the following criteria:<br>• Results in death<br>• Is life-threatening<br>• Requires hospitalisation or prolongation of an existing inpatient hospitalisation<br>• Results in persistent or significant disability or incapacity<br>• Is a congenital abnormality or birth defect<br>• Requires medical intervention to prevent one of the above, or is otherwise considered medically significant by the investigator (e.g. participant safety is jeopardised). |
| **Related SAE** | An SAE where there is a potential for there to be a causal relationship to the intervention. |
| **Related and Unexpected SAE** | A related serious adverse event that is also unexpected i.e. the nature, frequency or severity of the event is not consistent with what is expected for the intervention of study. |

## 4.2 Recording Adverse Events

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.

## 4.3 Reporting Serious Adverse Events to the coordinating centre

The assessment and reporting of SAEs and related SAEs will follow the relevant Warwick CTU SOPs.

Once a serious adverse event has been identified, information should be sent to the WCTU team at SIS@warwick.ac.uk, the WCTU QA team at WCTUQA@warwick.ac.uk and the Sponsor's Office at RGIT@imperial.ac.uk within 24 hours of the site becoming aware of the event. Reportable events should be recorded on the trial SAE form. The participant should continue to be followed-up until resolution of the event or a final outcome has been reached. Following reporting of a serious adverse event, any change of condition or other follow-up information should be reported by the same mechanism.

Events should be reported as a serious adverse event only if they:

- occur between randomisation and hospital discharge
- are serious (meet the criteria for Serious Adverse Events) AND are potentially related to trial participation, i.e. may have resulted from trial treatment;
- are not on the list of SAEs exempt from reporting (see section 4.3.1)

Examples of events that may be SAEs are;

- Use of one of the interventions causing a new injury that endangers the patient
- Unexpected cardiac arrest
- Sepsis related to use of collar
- Neuro-deficit

### 4.3.1 SAEs exempt from reporting

Some events are anticipated as a result of the injury that has led to immobilisation of the spine, rather than the immobilisation itself. Many will be hospitalised with some requiring a stay in ICU/HDU. The following events will not need to be reported to WCTU because they are recorded in the CRF as an outcome or are anticipated as a result of the spinal injury rather than the intervention being studied:

- wound/skin breakdown
- pneumonia/chest infection
- evidence of intercranial hypertension
- other events directly attributable as a result of the participant's spinal injury

## 4.4 Assessment of SAEs

For all reportable SAEs an assessment of the relationship between the SAE and the intervention should be done as per section 4.4.1 Assessment of causality.

### 4.4.1 Assessment of causality

Related SAEs are SAEs which are thought to have a potential for a causal relationship with the intervention. Causality should be assessed by a medical or clinical delegate of the PI at the investigator site. If an event is deemed to have a potential causal relationship, then this should be reported to WCTU via the mechanisms outlined in section 4.3. This should be followed by an expectedness assessment by an appropriately trained delegate of the Sponsor as per section 4.4.2 below.
The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form using the following descriptions:

| Relationship to trial medication | Description |
|---|---|
| Unrelated | There is no evidence of any causal relationship |
| Unlikely to be related | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment). |
| Possible relationship | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments). |
| Probable relationship | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |
| Definitely related | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. |

### 4.4.2 Assessment of expectedness

All related SAEs (Definitely, Probable or Possible) should be assessed against the known SAEs related to the intervention.
Expectedness assessment is the responsibility of the Sponsor and will be delegated to the coordinating centre in response to the causality assessments made by the investigator.

### 4.4.3 Expedited reporting of events to REC

The trial manager will liaise with the investigator to compile all the necessary information. The trial coordinating centre is responsible for reporting any related and unexpected SAEs to the sponsor and REC within required timelines. All other recruiting sites in the trial will be informed of the event and any implications for the trial.

All SAE reports will be reviewed on receipt by the Chief Investigator or Co-Chief Investigator (or their delegate). SAEs that are deemed to be unexpected and related to the intervention will be notified to the REC and sponsor within 15 days of receipt in accordance with regulatory requirements. All such events will be reported to the Sponsor, Trial Steering Committee and Data Monitoring Committee at their next meetings. Reports of all SAEs by randomisation arm will also be reviewed by the DMC at their regular meetings, or more frequently if requested by the DMC Chair.

## 4.5 Responsibilities

Principal Investigator (PI):

Checking for AEs when participants are reviewed or followed-up.

1. Using medical judgement in assigning seriousness and causality

2. Ensuring that all SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Immediate review of all SAEs
3. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
4. Production and submission of annual reports to the relevant REC.

Sponsor or delegate (WCTU):

1. Central data collection and verification of AEs, and SAEs, according to the trial protocol.
2. Expectedness assessment of related SAEs
3. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
4. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
5. Expedited reporting of related and unexpected SAEs to the REC within required timelines.
6. Notifying Investigators of related and unexpected SAEs that occur within the trial.

Trial Steering Committee (TSC):

In accordance with the Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Terms of Reference for the DMC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

### 4.6 Notification of deaths

Death is collected as a trial outcome and will be captured using the trial CRF.

### 4.7 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

## 5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with UK GDPR and Warwick SOPs.

Personal identifiable data will be held separately to trial data within the trial database, with linkage provided through a unique trial number.

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

## 5.1 Data management

Case Report Forms (CRFs) and a Progressive Web Application (PWA) will be developed to collect all required trial data. Where applicable, a random sample of at least 10% of CRFs will be checked, by the trial Research Team, against entries within the database and the source data for quality purposes. The percentage checked will be increased if a significant error rate is found. In addition, the first set of recruitment data collected from all new sites will be scrutinised.

### 5.1.1 Participant enrolment

The randomisation PWA will collect data relating to the management of the traumatic injuries sustained, the hospital the participant was taken to and participant characteristics. Local research teams, at the hospital the ambulance service delivers the participant to, will locate and follow-up the participant as appropriate.

### 5.1.2 In hospital through to discharge

For participants admitted to hospital a small amount of data will be collected on admission (FIM, ASIA neurological scale, analgesia given) by the local research team and at the point of hospital discharge. Data will be recorded using standardised case report forms (CRFs). Health-related quality of life will be collected using the EQ-5D-5L/EQ-5D-Y completed by the participant or, if they lack capacity, their consultee. The local research teams will be responsible for collecting this data.

At discharge FIM (completed by the appropriately trained clinical or research staff member), length of hospital stay, further treatment for spinal injury, discharge destination, and safety outcomes will be collected by the local research teams from the participant's medical records on the standardised trial CRFs. In addition, participants will also be asked to complete an EQ-5D-5L/EQ-5D-Y at discharge.

### 5.1.3 Follow-up

Survival status will be collected by hospital/Imperial research staff for all participants at 30, 90 and 180 days.

Following confirmation of survival status, participants will be followed up at 30 and 180 days and asked to complete two questionnaires. The participant may opt to complete these questionnaires by post, online or by telephone according to their preferences.

If the participant lacks capacity then a consultee may complete the questionnaires on their behalf. If the participant or consultee cannot be reached after 3 contact attempts no further attempts will be made on that occasion, however if they do not respond after 3 contact attempts at 30 days a further contact will be made (on up to 3 occasions) at 180 days.

For patients who have been discharged, a tele-video clinic or out-patient follow-up visit will be arranged for the patients (180 days post-randomisation) with the Imperial research team, where the FIM score will be documented, along with cost and resource utilisation and health-related quality of life (EQ-5D-5L/EQ-5D-Y). If the patient is still in hospital, a member of the local research team will aim to obtain their data by visiting them and if required, assisting them with the completion of this questionnaire.

To ensure accurate, complete and reliable data are collected the trial management team at WCTU and/or Imperial College London will provide training to site staff in the format of investigator meetings and site initiation visits. Quality assurance procedures will be put in place to ensure training is delivered in a standardised manner. The trial management team will provide the local Principal Investigators and research staff with training on the protocol, completion of the CRF and trial procedures including standard operating procedures.

## 5.2 Database

The trial database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff.

## 5.3 Data storage

All essential documentation and trial records will be stored by WCTU and recruiting sites in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

## 5.4 Data access and quality assurance

All data access will be controlled by individual usernames and passwords and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements. Staff will have access restricted to the functionality and data that are appropriate for their role and responsibilities in the trial, which is documented on the central coordinating delegation log. Any data that are transferred out of the secure environment (for example for statistical analysis) will adhere to Warwick SOPs.

## 5.5 Data Shared with Third Parties

The trial statisticians and DMC will have access to the dataset for the analysis of trial outcomes. Once the main analyses have been undertaken, de-identified individual participant data will be available to other investigators subject to approval of data analysis plans and compliance with the University of Warwick SOPs on Data Management and Sharing. Approval of data analysis plans will be the

responsibility of the TSC during the lifetime of the trial. Following study completion, the Chief Investigator and WCTU Data Sharing Committee will be jointly responsible for the approval of requests for data from other researchers. Approval will only be provided for proposals which are scientifically sound and have ethical approval. Data sharing agreements will be put in place for any sharing of the trial data. The trial will comply with Data Sharing Policies that may be instituted by the NIHR during the lifetime of the project.

### 5.6 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial in accordance with Sponsor guidelines.

## 6. STATISTICAL ANALYSIS

### 6.1 Power and sample size

Based on the pilot stage recruitment the planned sample size of this trial for the main study is 2010 patients (1005 per arm). This enables a loss to follow up of 20%. 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. 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, 80% power and two-sided 5% significance level (with loss-to-follow-up rate of 20%), we would require a total sample of 2010 patients. The sample size was informed using the following parameters:

1. Non-inferiority margin: Regulatory guidelines recommend defining the margin based on a review of historical evidence of the efficacy of the comparator[19,20]. The minimal clinically important difference (MCID) for the FIM-motor is not established for the spinal cord injury patients[21]. 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[22]. 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[24] also suggests that a 3-point non-inferiority margin can be considered for FIM-motor.
2. 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.
3. 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[25]. 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[26], 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 [27]. 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.

4. Loss-to-follow up rate: Using the NMTR data approximately 10% of patients die prior to hospital discharge. The LTFU rate is set at 20% including an additional 5% due to national data opt-out (10% death and 5% loss of primary outcome data at discharge)but we anticipate that it will be much lower, in keeping with the recently published CRASH-3 trial, which had a < 2% LTFU rate with a similar population and outcome assessment at discharge.

## 6.2 Statistical analysis of efficacy and harms

### 6.2.1 Primary outcome analysis

For the primary analysis, the difference in the FIM-motor score (and 95%) confidence interval will be derived using unadjusted and adjusted (for important covariates) analyses, using the linear regression models. In terms of interpretation, the intervention would be said to be not unacceptably worse than (i.e., non-inferior to) the control if, when the 95% CI around the difference in the effect size between the interventions is calculated and the lower bound of the interval does not extend beyond the -2.

A further exploratory analysis to assess the impact of missing outcome data on FIM-motor score will be examined using multiple imputation techniques.

### 6.2.2 Secondary outcome analysis

The continuous secondary outcomes will be examined using linear regression models (with point estimated and 95% confidence intervals). Categorical outcomes will be analysed using logistic regression models (OR and 95% CI of OR).

A detailed Statistical Analysis Plan (SAP) will be written by the trial statistician and approved by the DMEC prior to any interim analysis.

## 6.3 Subgroup analyses

Pre-specified sub-groups will include age (<65, ≥65 years old) and others which will be discussed with the Trial Steering Committee. Exploratory analyses will be reported using 99% confidence intervals. Logistic regression will be used with interaction terms (treatment group by sub-group) for the sub-groups selected.

## 6.4 Interim analysis and criteria for the premature termination of the trial

The timing and frequency of the interim analyses will be discussed and agreed with the Data Monitoring Committee members. It is anticipated that no more than one formal interim analysis will take place during the course of the study. The statistical stopping criteria will be formalised using the O'Brien and Fleming stopping rules[28]. In making a decision to terminate the clinical trial, the Data Monitoring Committee will use the statistical evidence as guidance to their decision making and will be also presented with a 95% confidence interval of the treatment difference.

### 6.5 Health Economic Evaluation

A prospectively planned economic evaluation will be conducted from an NHS and personal social services perspective, in accordance with an agreed Health Economics Analysis plan (HEAP). The methods will adhere to the recommendations of the NICE Reference Case[29].

Resource use will include intervention, hospital (ICU, HDU and ward days) and community costs (primary care and social care costs) in the 6 months following intervention. Resources will be costed using national reference unit costs where available, reflated to current prices.

Health-related quality of life (EQ-5D-5L/EQ-5D-Y) responses will be used to generate quality-adjusted life years (QALYs) using the value set recommended by NICE at the time of analysis[30] and area-under-the curve (AUC) method. The baseline EQ-5D-5L/EQ-5D-Y values will be imputed to reflect the unconscious health state and applied to all patients, minimising potential bias in the QALY AUC calculation36. Within-trial analysis (to 6 months) using bivariate regression of costs and QALYs will inform a probabilistic assessment of incremental treatment cost-effectiveness. Following best practice, missingness mechanisms will be explored, and multiple imputation methods will be used where appropriate to avoid biases associated with complete case analysis. Costs and outcomes arising during the trial will be undiscounted, reflecting the 6-month time horizon. Sensitivity analyses will be undertaken to explore uncertainty in the incremental cost-effectiveness and to consider issues of generalisability of the study.

Although not anticipated to be necessary, more extensive economic modelling using decision-analytic methods may be considered to extend the time horizon and decision context if costs and benefit profiles are non-convergent or non-dominant at 6 months. Such modelling will draw upon best available information from the literature and stakeholder consultations to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. Longer term costs and consequences will be discounted to present values using discount rates recommended for health technology appraisal in the UK (current discount rate: 3.5%)

## 7. TRIAL ORGANISATION AND OVERSIGHT

### 7.1 Sponsor and governance arrangements

Imperial College London will act as the Sponsor for the trial. All trial-related activity will be undertaken according to the principles set out in the Good Clinical Practice Guidance and in accordance with the UK Policy for Health and Social Care Research.

### 7.2 Ethical approval

Ethics committee review of the trial protocol and documents essential to the trial will be carried out by a UK NHS research ethics committee, flagged for studies involving adults lacking capacity. HRA approval will be obtained before the trial starts. Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has been reviewed by the relevant NHS Trust Research & Development (R&D) department.

Sites will not be permitted to enrol patients into the trial until written confirmation of the approval via the HRA and the confirmation of capacity and capability for the relevant participating Trust is received by the SIS trial team, based at WCTU.

Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC and HRA will be notified of any amendments, and once the trial concludes a final report will be provided in accordance with reporting requirements. In accordance with Warwick SOPs, the CI is responsible for making applications to the relevant authorities if an amendment to the research protocol or other trial document or process is required. The CI may designate a member of staff to prepare the amendment submission but retains responsibility for any amendment application, however, the CI is no longer required to sign the completed amendment tool but should be copied into any correspondence with the relevant sponsors' office. It is the sponsor's responsibility to assess whether an amendment is to be regarded as 'substantial' on a case-by-case basis and confirm their opinion with the CI or their delegate prior to any application being made. The sponsor is required to review and sign off the amendment tool prior to locking for submission. This will be returned to WCTU for submission and processing of the amendment. The WCTU trial management team will ensure that an impact assessment is carried out on all key trial documents (e.g. protocol, CRFs, data management plan, SAP, Risk Assessment and Monitoring Plan) to check if any associated documents require amending based on the proposed amendments to the trial.

As part of the funding decision by the NIHR HTA, the trial has been reviewed by both the HTA board and independent individuals with clinical, methodological, and patient involvement expertise. It is a requirement to send to the NIHR any protocol amendment documents for their approval prior to submission to the main REC.

## 7.3 Trial Registration

The SIS trial has been registered with the International Standard Registered Clinical Trial Number (ISCTRN) registry.

## 7.4 Notification of serious breaches to GCP and/or trial protocol

Deviations from the clinical trial protocol and 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.

A "serious breach" is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

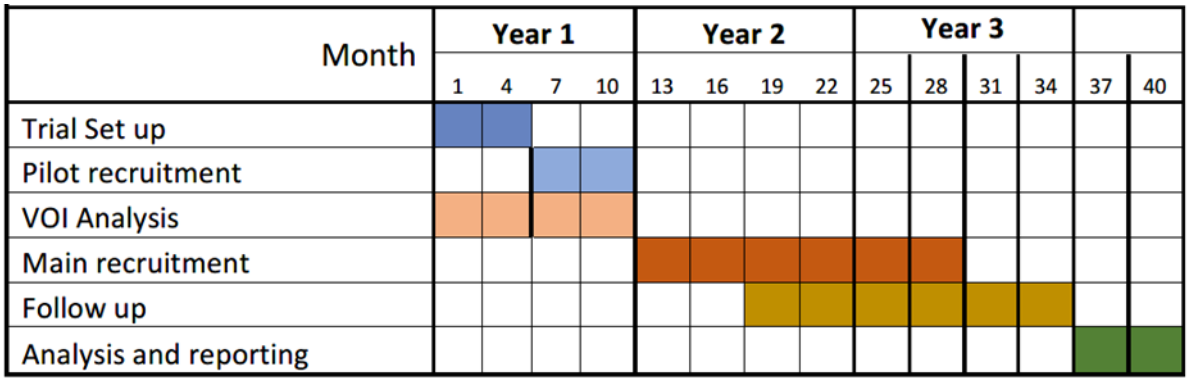
The sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

## 7.5 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this trial.

## 7.6 Trial timetable and milestones




## 7.7 Administration

The trial co-ordination will be based at Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick. WCTU has expertise in undertaking studies in emergency and critical care. The trial will be run to WCTU SOPs.

The WCTU will be responsible for protocol development, ethics and governance approvals, database development and data management, randomisation, trial management and monitoring, analysis of the data and reporting.

## 7.8 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or Investigators, as appropriate.

## 7.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one PPI representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

## 7.10 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant clinical research, and statistical experience. The DMC will meet at the end of the pilot phase regularly approximately every 6 months or so thereafter. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC as to

whether there is evidence or reason why the trial should be amended or terminated. In the unlikely event that the DMC recommends an early termination of the trial, whether due to safety concerns or for other reasons, a recommendation will be made immediately.

DMC meetings will also be attended by the Chief Investigator and Trial Manager (for non-confidential parts of the meeting) and the trial statistician.

The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

### 7.11 Essential Documentation

A Trial Master File will be set up according to the relevant WCTU SOPs and held securely at the coordinating centre.

The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

### 7.12 Financial Support

The trial is funded by the National Institute for Health Research (NIHR) HTA programme reference NIHR131430. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

## 8. MONITORING, AUDIT AND INSPECTION

A Trial Monitoring Plan will be developed by the trial team and approved by the CI, a member of the QA team and the Sponsor. A risk based proportionate approach will be outlined in the monitoring plan to facilitate remote and off-site monitoring if required.

## 9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

Two groups, ASPIRE (Association for Spinal Injury Research, Rehabilitation & Reintegration) and the Imperial PPI group were instrumental in reviewing and amending the proposal at the design phase and helped identify the FIM as the appropriate outcome measure for the trial. Additionally, consideration around the ethics of the trial (for example, consent waiver on scene) but subsequent consent when in hospital and the processes around this have shaped the trial to date and will continue to do so.

ASPIRE is a charity which supports around 50,000 people living with spinal injury in the UK. They will support the trial to ensure there is clear evidence in support of the most effective pre-hospital patient care, ensuring the best possible outcome for the patient.

The Imperial PPI group comprises spine and head injured patients and have experienced spinal immobilisation. The head injured patients experienced this when it was subsequently found to be unnecessary and therefore provide an important balance in the group.

The insight that service user representatives can offer from the patients' perspective complements the clinical expertise and specialist knowledge of the research team and will ensure that the trial maintains an approach which is centered on patients and their needs.

The PPI members will have input on the interpretation of the data at the end of the trial which will shape subsequent publications and, ultimately, guidelines. The PPI team will also be involved in the write-up of the outputs from this research and the dissemination of the findings.

## 10. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial coordinating team, and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org).

A communication strategy will be developed that involves all partners. The strategy will include identifying key stakeholders, messaging, channels for communication, coverage and frequency and potential risks and sensitive issues associated with the research. Dissemination activities will start as soon as we are permitted to share information about the trial. Audiences include patients and the public, clinicians (doctors, nurses and others), researchers and academic experts, policy makers (NHS England), national and international guideline groups, particularly those related to resuscitation. A series of outputs will maximise the impact of this research including conference presentations and other dissemination events.

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