accord
Academic and Clinical Central Office for Research and Development

NHS Lothian

Study Protocol

DENS

Duration of External Neck Stabilisation following odontoid fracture in older or frail adults: a randomised controlled trial of collar versus no collar

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DOCUMENT HISTORY

Version No	Date	Summary of Revisions
1.0	25 Mar 2021	Initial Protocol - Not implemented
2.0	19 July 2021	English REC - requested removal of the use of nominated consultees. Protocol not implemented.
3.0	04 Aug 2021	Study Title changed to long title. Addition of REC and project registration numbers. Addition of verbal consent for patients as well as patient representatives. Clarifications regarding screening log data, randomisation and follow up questionnaires. Removal of Urea and Creatinine from Baseline data collection. Clarifications surrounding CHI/Hospital number collection and storage. Patient diary and questionnaire time frames will be recorded from the point of randomisation. The patient diary data will only be available in paper format. Direct entry of follow up data to the database for patients only. Qualitative interviews will only take place over the phone. There will be no option for face to face interviews. Other typographical changes. Protocol not Implemented.
4.0	20 Aug2021	English REC requested removal of the word "following" from Section 2.2.1
5.0	07 Feb 2022	The Neck VAS completed at all follow ups has been replaced by the Numeric Pain Rating Scale (NPRS) to accommodate phone assessments. Section 6.4 Blinding of central research staff removed as this cannot be guaranteed. Addition of version table and a clearer image of Figure 2 - flowchart. Administrative corrections and clarifications.

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
CFS	Clinical Frailty Scale
CHI	Community Health Index
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CTT	Central Trial Team
DENS	Duration of External Neck Stabilisation
DMC	Data Monitoring Committee
ECTU	Edinburgh Clinical Trials Unit
ED	Emergency Department
EQ	EuroQuol
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
NDI	Neck Disability Index
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPRS	Numeric Pain Rating Scale
PI	Principal Investigator
PIP	Patient Identification Page
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PSS	Personal Social Services
QA	Quality Assurance

QALY	Quality Adjusted Life Years
QoL	Quality of Life
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIMD	Scottish Index of Multiple Deprivation
SOP	Standard Operating Procedure
TCC	Trial Coordinating Centre
TMF	Trial Master File
TMG	Trial Management Group
UK	United Kingdom
VAS	Visual Analogue Score

1 INTRODUCTION

1.1 BACKGROUND

The odontoid process is a bony protuberance from the body of the second cervical vertebra in the neck. (Figure 1) Fractures of the odontoid, also known as the dens, can occur following low impact falls in frail and older people, (1) and are increasing in incidence as the number of older people in the population increases.(27) The Trauma Audit and Research Network database identified an annual incidence of at least 1,700 odontoid fractures in the United Kingdom (UK), 85% of which were in people aged over 65 years.

Anderson and D'Alonzo classified three types of odontoid fracture based on the location of the fracture within the odontoid (Figure 1).[1] Type I fractures occur through the odontoid tip, type II fractures occur through the base of the dens, and type III fractures extend into the body or lateral masses of the second vertebra. Type II fractures are the most common (>50% of all odontoid fractures), and have the lowest rates of bony fusion.[1]

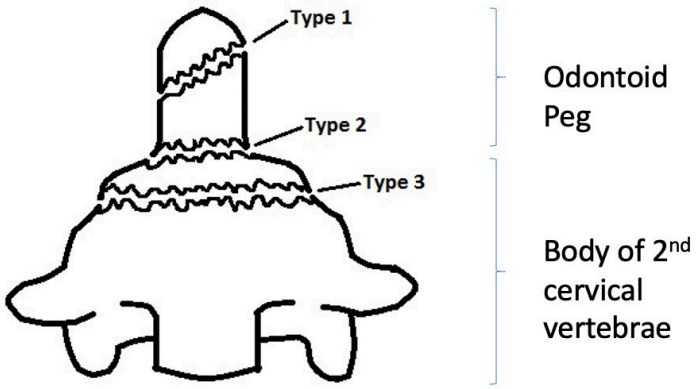


Figure 1. Classification of odontoid fractures Type 1-3. The second cervical vertebra is drawn in a front projection and the odontoid peg (dens) projects from upper part of the body. (https://dx.doi.org/10.1594/ecr2015/C-1336)

Functional outcomes are similar across all odontoid fracture types and treatment methods.[2] In frail or older people, usual care for odontoid fractures in the UK is non-operative in 85-90% of cases, regardless of the fracture type.[3–5] Non-operative care usually constitutes immobilisation in a cervical hard collar 24 hours a day, 7 days a week, for 12 weeks. This aims to promote bony fusion to prevent neurological deterioration and pain from instability.[3–6] However, hard collars restrict only 40-50% of neck movements,[7] and bony fusion rates vary from 20-80%.[3,4,8] Instead, stable fibrous non-union occurs in 60-80% of odontoid fractures managed in a hard collar[2,9] Despite the lack of bony fusion, neurological deterioration is very rare in older people.[4,8,10] Stable fibrous non-union is therefore an acceptable patient outcome in older and frail people.[2,9] Importantly, the presence of bony fusion is not associated with improved pain, quality of life, or reduced mortality at one to five years follow-up.[2,9,11,12]

Hard collars can cause pressure ulcers and difficulty with eating, personal care and activities of daily living, impacting quality of life.[12] Additional health and social care input is often required to assist patients wearing a hard collar, because of the restrictive effect it has on neck movements and consequently on activities of daily living.

If bony union is unnecessary for acceptable patient outcomes, and collars can negatively impact quality of life (QoL), then perhaps management with a collar is unnecessary and may cause additional harm. Maximising short-term quality of life rather than aiming for long-term radiological outcomes, or prevention of unlikely future deterioration, may be more important in a frail older population with a shorter life expectancy. At one year following an odontoid fracture mortality is 20-40%, reflecting a patient's underlying health status and frailty, rather than the fracture itself.[6,10] Functional impairment and immobility consequent to the hard collar may be an additional contributor to mortality.

There is a lack of clear evidence in this area as determined by a search. On the WHO international clinical trials registry platform, the ISRCTN registry, the EU clinical trials registry and ClinicalTrials.gov, where there are no completed or ongoing trials investigating management without a collar for older frail people with odontoid fractures. Whilst there are five trials comparing surgical fixation to non-surgical management in older or frail patients with odontoid fractures, there were no previous or ongoing studies comparing a hard collar with no collar in such patients.

In our survey, 91% percent of 43 UK spinal surgeons would randomise older patients with odontoid fractures to management with or without a collar, to find out whether the collar is necessary. Feedback from older patients managed in collars is that they are keen for treatment options without a collar if possible.

1.2 RATIONALE FOR STUDY

The Duration of External Neck Stabilisation (DENS) study is a randomised controlled trial comparing early removal of a hard collar with treatment in a hard collar for 12 weeks in older or frail adults with odontoid (dens) fractures. The primary outcome measure is QoL assessed using the EQ-5D-5L at 12 weeks following randomisation. The aim of the study is to determine whether management without a collar improves outcome, compared to management with a collar. Cost efficiency will be assessed over the observed 12 months using standard NICE reference case methodology.

1.2.1 Importance of the Question

Establishing the most appropriate management of odontoid fractures in older or frail people is of increasing importance in an aging UK population where low impact falls are now the most common mechanism of trauma. The complications of hard collar use [12] and the lack of benefit of bony union on QoL, pain, or neurological outcomes,[2,9] provide a strong impetus to ask whether management without a collar is preferable.

We hypothesise that early removal of a hard collar will have a positive impact on QoL and be associated with a more rapid return to baseline level of function and independence, whilst avoiding treatment related complications. This is an opportunity to make a positive impact on QoL whilst creating savings in hospital, rehabilitation, and community care.

1.2.2 Current Treatment Options

Odontoid fractures are identified on cervical spine radiographs and Computed Tomography (CT) images in patients following trauma. Options for management of odontoid fractures

include surgical fixation, or external immobilisation. Surgical fixation is most appropriate in high-impact trauma in younger patients to facilitate bony fusion and to prevent neurological deterioration. In older and frail adults, surgical fixation may improve rates of radiological bone fusion[11] but is not associated with improvement in functional outcomes.[13] Moreover, complication rates following surgery are high in this population.[3] In the UK surgical fixation is rarely offered to older or frail adults (defined below) as the risks are felt to outweigh the benefits.

Non-surgical options for odontoid fractures include halo fixation, hard collars, or soft collars. Halo brace immobilisation, where a metal ring is screwed into the skull and fixed by rigid bars to a vest, is rarely used in older patients with odontoid fractures, as complications are common, without improvement in bony union or functional outcomes compared to a hard collar.[3] Soft collars are used at least some of the time by fewer than 10% of UK spinal surgeons for odontoid fractures,(3) provide minimal restriction of neck movements,(39) and are not useful in managing neck pain.(40) They may still be associated with collar-related complications such as dysphagia or skin breakdown. Therefore, in the UK, most odontoid fractures in older and frail people are managed using hard collar immobilisation.

Although there have been no previous trials of odontoid fracture management without neck immobilisation, UK spinal surgeons responding to a survey reported they would currently manage these fractures without external immobilisation if the patient was unable to tolerate the collar or was distressed by it (90%), had a short life expectancy (65%), or if complications such as skin breakdown or cardiorespiratory disease occurred (77-80%). Therefore, some frail patients with odontoid fractures are already being managed effectively without any immobilisation.

1.2.3 Study Intervention

Older and frail patients with a new odontoid fracture will be randomised to continuing in a hard collar for 12 weeks or to early removal of the hard collar.

In current standard care, patients with suspected cervical spine injuries are usually immobilised with non-padded trauma collars or blocks, possibly on spinal boards, on admission to the emergency department (ED). Early removal of an emergency immobilisation and replacement with a padded hard collar (e.g. Miami J, Aspen, Philadelphia) as per standard care is desirable for skin care and comfort.

Some clinicians question whether cervical spine immobilisation is necessary in alert trauma patients and so it is not universally applied. Some patients may therefore not be in a collar prior to randomisation in the study. If emergency mobilisation is not employed, then a hard collar may be applied if randomisation cannot occur straight away.

1.2.4 Measurement of Outcomes

Quality of life (QoL) measured with the EuroQuol (EQ) EQ-5D-5L tool is our primary outcome measure with the neck disability index (NDI) as a secondary neck specific outcome measure. The 12-week primary outcome period reflects the standard care treatment duration in a hard collar. An earlier time point may reflect the acute injury rather than its management, and later time points may reflect the impact of overall frailty rather than injury management.

The EQ-5D-5L has two parts. The self-classifier asks patients to describe their health in terms of the level of problems. The EuroQol-visual analogue scale (EQ-VAS) component is a vertical visual analogue scale that takes values from 100 (best imaginable health) and 0 (worse imaginable health), on which patients provide a global assessment of their health and is an important adjunct to the EQ-5D-5L questionnaire. The minimum clinically important difference in EQ-5D-5L that we are investigating is 0.05, based on the widespread literature of studies using EQ-5D.

The assessment of whether management without a hard collar is more beneficial for overall QoL requires that the study outcome measure is of importance and relevance to the frail older population. It should be easily completed and be sensitive to differences in this population. There are no established core outcome sets for cervical spine fractures in older people (COMET database).

The most used preference-based measure of QoL in both community and institutional dwelling older adults is the 5 item EQ-5D-5L. A review of 53 patient reported outcome instruments from 241 studies of degenerative cervical spine surgery recommended the EQ-5D for general health assessment, as it covered the most important health related QoL dimensions for musculoskeletal disease.[14] A systematic review examining the extent to which the EQ-5D can detect a clinically significant change over time or across different disease domains, found EQ-5D was responsive in 25 of 56 specific conditions assessed, including acute whiplash, surgery of the neck and cervical spine injury. Although ceiling effects have been reported with the EQ-5D in younger and healthier populations,[15] this is not the case in older patients with morbidity such as our study population, and is less of a problem with the use of EQ-5D-5L which has 5 options per dimension rather than the three of the EQ-5D-3L.[16] The EQ-5D-5L was found to be responsive to a clinically significant change in cervical spine injury. Compared to other preference-based instruments EQ-5D is easier to administer, has a validated option for proxy completion, has a higher completion rate and performs well in older patients with a high construct validity, including those with cognitive impairment.[17]

The NDI is a specific functional outcome measure for neck pathology. It is a secondary outcome measure in our study. The NDI has been shown to be reliable and valid in younger degenerative spinal surgery population. Some of the domains such as driving, and work may be less relevant to older or frail adults or those immobilised in a collar. The Numeric Pain Rating Scale (NPRS) provides a global assessment of symptom control to support the functional data from NDI. Other secondary outcome measures (detailed in Section 2) include mortality, adverse events and late-injury complications, to identify any safety issues with either the hard collar or its early removal. No adverse events have been reported when older or frail patients with a new odontoid fracture are managed without a hard collar.

Both older people with odontoid fractures and members of a Patient and Public Involvement (PPI) group preferred the EQ-5D-5L as the primary outcome measure because of its ease of completion, and relevance. It is the preference-based measure preferred by the National Institute of Clinical Excellence (NICE) guide for health technology assessment and can produce preference-based health related QoL weights for economic evaluation, which is a core component of translating clinical trial outcomes into routine care.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To determine difference in quality of life, assessed with the EQ-5D-5L, at 12 weeks, between the no collar (intervention) and collar (standard care) arms.

2.1.2 Secondary Objectives

To establish differences between the two arms in:

- NDI, Numeric Pain Rating Scale (NPRS) and EQ-5D-5L scores up to one year following treatment
- Mortality at 6 and 12 months
- Adverse events up to 12 weeks (including neurological deficit, aspiration pneumonia, delirium, pressure sores, swallowing problems)
- Length of primary admission and discharge destination
- Loss of muscle bulk in upper limbs over 12 weeks
- Repeat hospitalisations (including outpatient visits) and total inpatient bed days, up to 1 year
- Health care, community health and social care use, and primary care visits up to 1-year based on patient questionnaire feedback and local research team assessment
- Regular analgesia use up to 12 weeks
- NHS costs, Quality Adjusted Life Years (QALYs), and cost-utility from an NHS and PSS (personal social services) perspective up to one year
- In fracture site bony fusion and stability at approximately 12 weeks assessed on imaging (CT, flexion-extension x-rays or MRI) where performed as part of standard care
- Compliance with study allocation
- Late injury-related complications, such as new neurological deficit, up to 1 year post randomisation

To investigate:

- Whether frailty, age, deprivation index (Scottish Index of Multiple Deprivation, SIMD), fracture type (I-III), or bony fusion/stability affects the primary outcome
- Tolerance and compliance with collar

2.1.3 Qualitative study objectives

Nested qualitative research will be undertaken during the trial's pilot phase to address the following aims and objectives:

Aims

(1) To understand and explore trial recruitment experiences from the perspectives of patients, caregivers (if the patient is unable to give informed consent) and health professionals
(2) To explore whether, and why, patients do/do not adhere to the intervention (early removal of a hard collar) or standard care (hard collar for 12 weeks)

Objectives

- To inform refinements to the recruitment/consent pathway used in the trial, if required
- To offer insights which can be used to aid trial retention
- To aid interpretation of trial results

2.2 ENDPOINTS

2.2.1 Primary Endpoint

EQ-5D-5L score at 12 weeks post randomisation

2.2.2 Secondary Endpoints

- NDI, Numeric Pain Rating Scale (NPRS) and EQ-5D-5L at baseline, 2, 6 and 12 weeks, 6 months and one year post randomisation
- Mortality at 6 and 12 months
- Adverse events at 2, 6 and 12 weeks
- Length of primary hospital stay and discharge destination,
- Mobility and use of walking aids assessed by questionnaire at 2, 6 and 12 weeks, 6 months and one year post randomisation
- Changes in grip strength and muscle bio-impedance as indicating muscle bulk over 12 weeks
- Repeat hospitalisations (including outpatient visits) and total inpatient bed days, up to 1 year assessed by questionnaire
- Heath care, community health and social care use and primary care visits at 2, 6 and 12 weeks, 6 months and one year post randomisation assessed by questionnaire
- Medication diary reporting regular analgesia use from the time of randomisation to 12 weeks
- NHS costs, Quality Adjusted Life Years (QALYs), and cost-utility from an NHS and PSS (personal social services) perspective
- Differences in reported bony fusion and stability at 12 weeks on imaging (e.g. CT, flexion-extension x-rays or MRI) where performed as standard care
- Compliance with study intervention allocation (measured with iButtons for collars – see Section 3.1.1, and patient diary for all patients, which will accompany medication diary)

3 STUDY DESIGN

This is a non-blinded randomised controlled trial with nested qualitative research comparing early removal of a hard collar (intervention) with treatment in a hard collar for 12 weeks (standard care) in older or frail adults with odontoid peg fractures. The primary outcome measure is QoL assessed using the EQ-5D-5L at 12 weeks following randomisation. (Figure 2) The study will run for 48 months from 1st February 2021.

The clinical team will identify potentially eligible patients presenting acutely with odontoid fractures to the Emergency Department (ED) at the time of admission, based on a CT cervical spine reports, and from referrals and admissions to spinal services. Patients may also be identified by the Medicine for the Elderly team. We will give recruiting centres posters to make potential patients aware of the study.

Potentially eligible participants will be assessed in the ED, or on hospital admission. Assessment of eligibility, recruitment and randomisation should take place as soon as

possible (target within 48 hours) after injury. Patients with incapacity who are unable to give informed consent may still be recruited.

Exceptionally, patients who have not been assessed for eligibility at the time of their acute admission, or who were assessed but in whom there was some other delay to study inclusion, may be recruited up to 3 weeks post-injury.

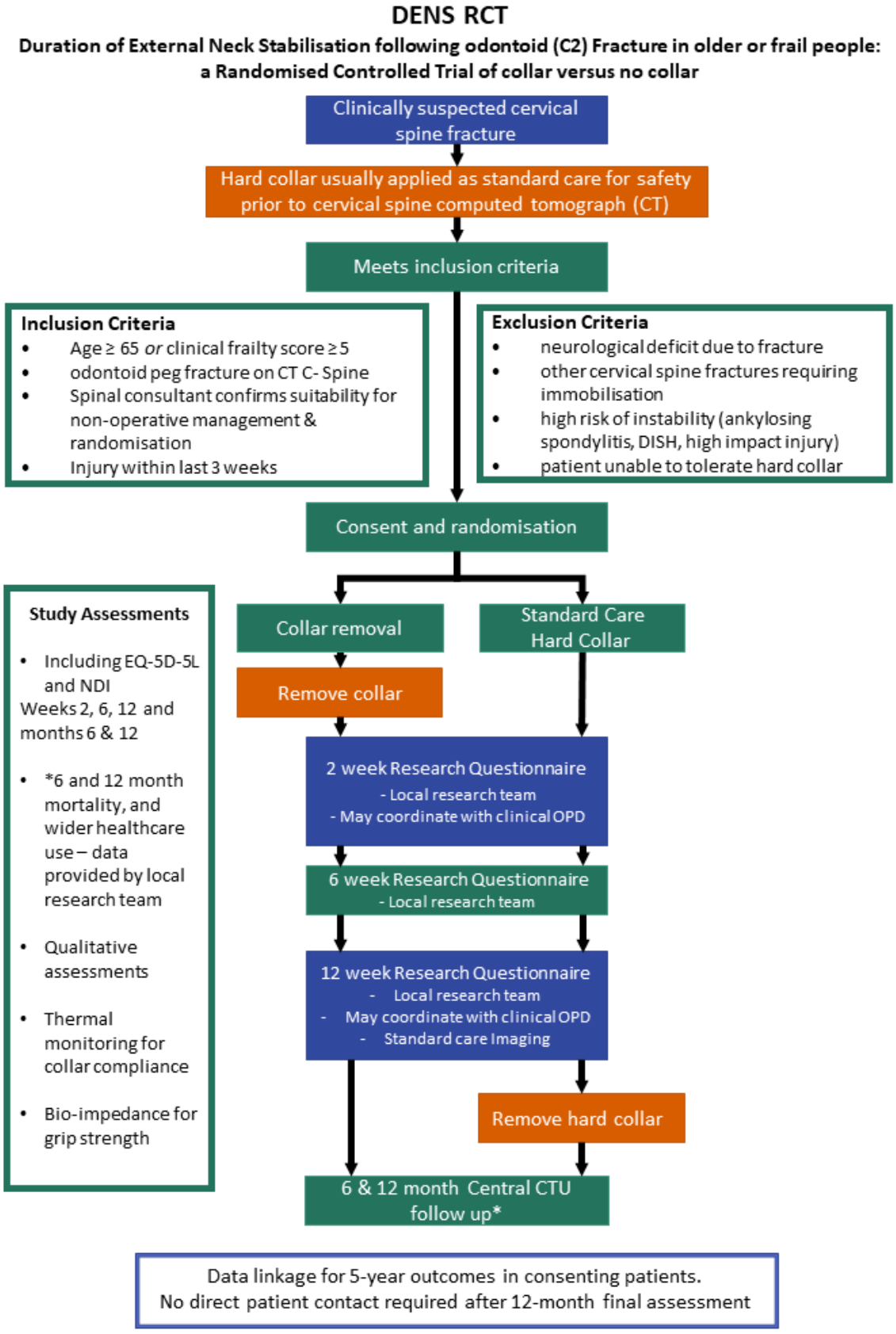
Those who take part will be randomised to continuing in a hard collar for 12 weeks or to early removal of the hard collar.

During the pilot phase, a subset of patients, caregivers and health professionals will be interviewed.

In current standard care, patients with suspected cervical spine injuries are usually (but not universally) immobilised with non-padded trauma collars or blocks, possibly on spinal boards, on admission to the ED. Early removal of this emergency immobilisation and replacement with a padded hard collar (e.g. Miami J, Aspen, Philadelphia) as per standard care is desirable for skin care and comfort. In this study this immobilisation replacement will take place as usual with guidance from ED and spinal service (orthopaedic/neurosurgical) on-call staff, according to local protocols. This avoids any delay in removal of emergency immobilisation that might be caused by trial procedures to establish eligibility or consent that could lead to poorer quality of care for participants.

All participants will undergo standard care investigations for suspected cervical spine fracture. This includes CT of the cervical spine to identify fractures, and a full neurological examination and assessment. All participants will be discussed with the on-call spinal (neurosurgical/orthopaedic) service unit as per usual protocols. All participants will be given adequate analgesia for neck pain. Participants will only be enrolled following a consultant radiologist report of an odontoid fracture and confirmation from the local spinal consultant that randomisation to non-operative management with or without a hard collar is appropriate.

Figure 2. Flow chart of patient screening, randomisation, and follow up



Assessment of eligibility, recruitment and randomisation should take place as soon as possible (target within 48 hours) after injury. We recommend that in a patient with the capacity to consent, a decision should be made as soon as possible, and within 72 hours of information being provided to them.

Patients with incapacity who are unable to give informed consent can still be recruited. We will actively facilitate inclusion of patients with dementia, cognitive impairment, or significant frailty as these are patients at high risk of odontoid fractures from low impact falls, and at high risk of complications from collar use.

The majority of patients attending the ED who are found to have an odontoid fracture will in fact have an associated medical or trauma catastrophe (i.e. syncope/collapse/fall etc) associated with it. These factors, the pain, anxiety, effects of the acute environment and discomfort around initial collar management associated with the diagnosis and fracture will mean that most of these patients will not have capacity and may not have capacity to weigh up the pros and cons of the study for some time after the event. We recommend enrolment of patients as early as possible after assessment of eligibility to maximise impact of the study intervention, even if they lack capacity.

Few frail and older patients with new odontoid fractures are discharged directly from the ED, because falls in older people are often multifactorial and acute medical issues (e.g. sepsis) may require treatment.[18] Additional home support for collar care may need to be arranged. Potentially eligible participants can therefore be approached for recruitment at any time within 3 weeks after injury whether they have been treated with a hard collar in the first instance. Participants who have been discharged can be recruited during outpatient follow up at either their local spinal centre or their local hospital if they are within 3 weeks of the injury.

Whilst we are prioritising randomisation of patients as early as possible after their fracture diagnosis, the 3-week cut off period maximises participation by providing flexibility to fit within NHS acute care pathways, facilitates participation in those who are acutely unwell at participation or who might otherwise be excluded, and ensures safety by ensuring there is time for full assessment against inclusion and exclusion criteria.

Those randomised to a hard collar will continue with approximately 12 weeks of treatment in a hard collar in alignment with standard care in the UK. Adequate personal care will be arranged according to local pathways. For these patients in the standard care arm of the study, the patient's spinal surgeon will ultimately determine when the hard collar should be removed, based on the standard care pathway in their Unit. If they determine that earlier collar removal is necessary after randomisation to the standard arm of the study, before 12 weeks post-injury, then the reasons for this will be recorded and the patient will continue in the study unless they request to withdraw.

Patients randomised to early removal will remove their collar as soon as possible. Collar use may be weaned (e.g., over 2-3 days) if required for pain control despite pharmacological analgesia. The time of cessation of collar removal will be recorded. Soft collars should not be used in either treatment arm.

3.1 QUALITATIVE STUDY DESIGN

The qualitative interviews and data analysis are being led by study team members Professor Julia Lawton and Dr Helen Eborall of the Usher Institute, University of Edinburgh.

Aim 1: To understand and explore trial recruitment experiences from the perspectives of patients, caregivers (if the patient is unable to give informed consent) and health professionals.

To address Aim 1, health professionals (~n=20) involved in recruitment will be interviewed to explore: what did and not work from their perspectives; perceptions and understandings of why patients/caregivers did/did not give consent for trial participation; their views about how trial recruitment approaches and materials could be refined and/or improved; and (if relevant) reasons for not approaching/recruiting certain types/groups of individuals meeting trial inclusion criteria. Patients/caregivers (if patient is unable to give informed consent to take part in the trial) (N=30) will also be interviewed to understand and explore reasons for taking part/declining participation; and, views about trial recruitment approaches and materials used and how these could be improved to aid understanding and willingness to participate.

Aim 2: To explore whether, and why, patients do/do not adhere to the intervention (early removal of a hard collar) or standard care (hard collar for 12 weeks)

To address Aim 2 interviews will be undertaken with patients/caregivers following randomization to explore initial reactions to being allocated to the control/intervention arm, hopes and expectations regarding trial participation; and any anticipated difficulties or concerns adhering to collar/no collar treatment. Follow-up interviews will be undertaken with the same individuals at the end of the intervention component of the trial (i.e. 12 weeks later) to explore whether, to what extent, and why, they did/did not adhere to collar/no collar treatment, perceived benefits/burdens of using/not using a collar; and, their perceptions of the impact of the intervention/standard care treatment on quality-of-life and recovery.

Note: where possible the same patients/caregivers will be interviewed to address study aims 1 and 2.

Sample
Health professionals will include Emergency Department, Orthopaedic, Neurosurgical and Medicine of the Elderly medical staff, at training and consultant grade, along with nursing staff and research nurses in these specialities, and will be sampled from a cross section of trial sites involved in the pilot phase.

Patients/caregivers will also be sampled from the cross section of sites involved in the pilot phase. Purposive sampling will also be used to ensure representation of individuals of different ages, socio-economic backgrounds, cognitions (e.g., able or unable to give informed consent), and living in different settings/circumstances (e.g., living alone, with a partner or in a residential home). Sampling decisions may also be revised considering emerging findings.

Recruitment
Patients/ caregivers of patients who are unable to consent for themselves, will be consented into the qualitative research at the same time as they are consented into the trial.

A recruitment pack (containing a covering letter, participant information sheet and an opt-in form (with prepaid envelope), will be given to individuals who decline trial participation by the health professionals involved in recruitment. The opt-in form will be directly returnable to the qualitative research team.

The trial manager supported by the local PI at participating sites will identify staff who have been involved in recruitment to the study. A recruitment pack (containing a covering letter, participant information sheet and an opt-in form (with prepaid envelope), will be mailed or emailed to health professionals by the qualitative researcher. The opt-in form will be directly returnable to the qualitative research team.

Data collection
Interviews will be informed by topic guides, which will be developed considering literature reviews, study research questions and input from our interactive working group; these will also be revised in light of ongoing analysis and emerging findings. Interviews will be carried out over the phone and will be digitally recorded (with consent), using a device encrypted to AES256 standard.

Translation of qualitative findings into recommendations to improve trial conduct:
An interactive working group will be set up for this study, comprising the qualitative research team, coinvestigators, the trial manager, PPI reps, and at least one health professional from each of the sites involved in the pilot phase, who will bring their experiences of trial recruitment and delivery to the group for discussion. This group will be convened at roughly 2 monthly intervals during the pilot phase, and at 3 to 4 monthly intervals thereafter and we will use a 'what, so what, now what' approach to translate qualitative findings and other experiences shared by group members into tangible recommendations to improve trial conduct (e.g., recruitment approaches).

3.2 ADHERENCE AND COMPLIANCE WITH COLLAR USE

All patients in the study randomised to standard care collar use will complete a patient diary of daily collar use. In some patients (N=20-30) we will validate these observations. Several types of devices have been employed for direct monitoring of compliance in patients wearing orthoses such as cervical hard collars, including strap tension monitors, pressure sensors and temperature-time sensors.[19] In our study compliance with collar use will be assessed in 20-30 of the first patients recruited using Thermochron iButtons (Measurement Systems Ltd, Berkshire, UK). These miniature and inexpensive temperature loggers are 10p-sized devices [20] with an internal battery, and resolution to 0.5degress Celsius. They are each launched using free software, and 'missioned' with an iButton reader that attaches to a computer.

Recruitment
Patients will be selected for the iButton based on i) randomisation to standard care collar use ii) location in one of the principal units included in the pilot phase of the study and iii) being one of the first approximately 20-30 patients randomised to standard care in these sites.

The iButtons will be missioned by the central study team and have an anonymous ID so the data generated is not identifiable. The iButton will be placed in the foam insert of the hard collar, as previously described, to record variation in temperature and so to identify compliance with usage until the collar is mandated to be removed by the patient's supervising spinal surgeon, which in standard care is after 12 weeks from the injury. The iButtons will be returned to the TCC when the collar is removed at the end of the standard care treatment, using a prepaid envelope provided to the patient. The data will be assessed to determine from the temperature readings (body temperature versus room temperature) whether the collar was not worn for any portion of the day. This will be correlated to the patient diary, where the patient will have confirmed daily collar use.

Patients randomised to the standard care arm, but who do not receive an iButton, will be assessed for compliance with their collar diary alone.

The impact of collars on QoL between the study arms will be interpreted with reference to this assessment of compliance, as well as feedback from the qualitative study.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

The intervention study will recruit a target of 887 participants from approximately 25 sites. Recruitment is expected to run for 2 years.

4.2 INCLUSION CRITERIA

The inclusion criteria are:

- Rockwood clinical frailty scale (CFS) of 5 or more, or aged 65 years or over;
- A recent odontoid fracture (type I-III) (within 3 weeks) as assessed on CT, irrespective of degree of fracture angulation, displacement or canal narrowing;
- History of recent trauma (within 3 weeks)
- Determined by spinal consultant (or delegated registrar) as suitable for standard care 12-week treatment with hard collar and for randomisation to treatment without a collar; and
- Recruited within 3 weeks of injury

There are no additional costs for patients associated with trial participation.

We will actively facilitate inclusion of patients with dementia, cognitive impairment, or significant frailty as they are most likely to benefit from this study. Participants who have acute confusion or delirium will be eligible to participate.

Patients with additional (non-odontoid) cervical spine fracture will be eligible provided the fracture(s) are suitable for management without a hard collar, in the opinion of the spinal consultant. Participants who have sustained other injuries, such as fractured femurs, or head injuries, will be eligible to participate.

For the Qualitative studies that do not involve recruited patients, inclusion criteria are:

- Any healthcare professionals involved in patient recruitment may be asked by their local PI in participating research centres
- Any carer of a patient unable to give informed consent from a participating centre may be asked by the local research team if they wish to participate
- Any patient eligible for DENS RCT who declines participation in the trial may be asked by the local research team if they wish to participate

4.3 EXCLUSION CRITERIA

The exclusion criteria are:

- Fracture sustained in high-impact injury;
- New neurological deficit (numbness / weakness) attributable to fracture;
- Assessed as unable to tolerate a hard collar e.g., dystonia, fixed deformity;
- Additional (non-odontoid) cervical spine fracture not suitable for management without a hard collar;
- Underlying condition potentially leading to spinal instability, e.g., ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis (DISH);
- Fracture suspected to be older than three weeks at the time of assessment;
- Consultant spinal surgeon determines fracture requires surgical treatment or is otherwise unsuitable for non-surgical treatment with or without a hard collar;
- Fall from more than 6m, patient ejection from vehicle, death in same vehicle, vehicle versus pedestrian (patient), vehicle versus cyclist (patient)
- If not expected to survive to hospital discharge based on concomitant injuries or illnesses.

4.4 CO-ENROLMENT

Co-enrolment will normally be permitted to CTIMP, and non-CTIMP observational and diagnostic studies where this does not affect the DENS study randomisation allocation or outcome measure assessment, and where doing so is not expected to burden the participant.

CTIMP with Non-CTIMP Co-enrolment
Participants who are active in the interventional phase of a non-CTIMP can be co-enrolled to a CTIMP provided the CTIMP/non-CTIMP Co-enrolment Checklist (POL008-F02) is completed by the Sponsor Representative(s) in conjunction with the CI prior to the co-enrolment proceeding. Co-enrolment with a non-interventional research (e.g. sample only, questionnaire studies) will not typically require any formal documentation or authorisation from the Sponsor.

Non-CTIMP Co-enrolment
Arrangements for co-enrolment with another interventional non-CTIMP will be permitted in compliance with the study protocol. Written agreement in the form of email communication is required from both Cis and must include a statement on the impact on participant burden and study outcomes as a minimum. Co-enrolment between non-interventional research (e.g. sample only, questionnaire studies) will not typically require any formal documentation or authorisation from the Sponsor.

Sponsor guidance available here: http://www.accord.scot/sites/default/files/POL008%20Co-enrolment%20v1.0.pdf

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Research staff participating in patient identification should be a part of the clinical team responsible for or contributing to the patient's care. These include Emergency Department, neurosurgical, orthopaedic, acute medicine and elderly care doctors, nurses, research nurses and allied health professionals.

There are multiple overlapping mechanisms to allow identification of patients for eligibility assessment. Day-to-day clinical practice of research staff may identify potentially eligible patients. Patients may also be referred for eligibility assessment by other clinical staff who are not part of the research team.

At each study site, the research team may include:

- Principal investigator (PI) - lead clinician at a participating site
- Delegated physicians – clinicians with delegated roles within the trial
- Local coordinator – lead member of research staff at a participating site
- Local research staff – staff members supporting the principal investigator and delegated physicians

5.1.1 **Sources of patient** identification

Potentially eligible patients will be identified through screening of ED attendances, acute hospital admissions, and spinal (orthopaedic or neurosurgical) referral databases by clinical teams and the local research team (where they are part of the clinical team). Patients will be screened for eligibility in the ED or other acute assessment areas, in hospital, or at an early clinic review, within 3 weeks of injury. Information from the hospital records may be used to assess eligibility against inclusion and exclusion criteria. Early screening maximises time for patients or their representatives to consider the trial materials and to enquire should clarification be needed. We will give recruiting centres posters to make potential patients aware of the study.

We will ask clinical teams and local research teams (where they are part of the clinical team) to screen for eligibility in patients with ANY new cervical fracture. This will minimise the chance of overlooking a potentially eligible patient where an odontoid fracture was noted in the radiology report, but not documented by the clinical team in the patient record.

It is a common referral policy to discuss any patient with a new diagnosis of cervical spine fracture with the local spinal team. Spinal (orthopaedic or neurosurgical) units will have their own referral log, which will serve as another source of patient identification.

Most patients will receive acute care remote to the spinal unit, although patients may be transferred to a spinal unit for care, where this is directed by local protocols. In this case eligible patients can also be identified from spinal unit daily admission logs.

5.1.2 Screening Log

Each participating centre will collect details of non-identifiable potentially eligible patients along with any reasons for exclusion. These details can be entered directly to a standalone area of the database or centres can complete a paper screening log and update these details to the database on a regular basis. This will be analysed to assess whether the recruited participants are representative of the potentially eligible population, and whether there are regional or temporal differences in patient recruitment.

5.2 CONSENTING PARTICIPANTS

5.2.1 Responsibilities

Once eligibility has been confirmed, an appropriately trained member of staff on the delegation log is responsible for obtaining informed consent from patients or from their representatives (where the patient does not have capacity to consent). The informed consent form (ICF) must be complete, signed and dated by all parties. In the case where patients have capacity but are unable to write due to physical restrictions, then a witness can sign on their behalf. (Randomisation will occur online once the ICF is completed. The ICF hard copy will remain in the local site file.

5.2.2 Process

The consent process must include adequate oral and written information. The staff member obtaining consent should explain all relevant information, (almost always face to face, but may in view of COVID-19 pandemic restrictions be done via the telephone), which is in line with the appropriate participant information sheet (PIS) and the ICF. Every opportunity should be given to the patient for clarification of information and, if necessary, for them to ask for further information. The right to withdraw consent to participate at any time should be explicitly specified, and this would not change the care that is received. The patient or their representative should not be put under time pressure and will be given the time needed to consider giving consent for the trial.

After as long as they require to consider participation in the study (up to 3 weeks post injury) and the opportunity to ask questions, participants will be asked to provide written consent.

5.2.3 Documentation

An informed consent form is considered valid and complete if signed and dated by both the participant or their representative, and a member of the study team on the delegation log. Written informed consent should be sought from the participant where possible, but verbal consent (including consent taken over the phone) from a participant or their representative, signed and witnessed by members of the study team, will also be valid. If the participant is unable to write, the member of the study team can also gain witnessed verbal consent.

The original ICF is stored in the local investigator site file along with the PIL and randomisation form. One copy of the ICF should be given to the participant or their representative; one filed in the patient's medical records. The staff obtaining consent should document the consent process in the participant's medical records for any future source data verification. The minimum requirement of this documentation should include the date of consent, provision of PIL, name of staff obtaining consent, name of patient's

representative if applicable, and confirmation of eligibility for trial enrolment with signatory and date.

The participant's GP will be notified of the trial enrolment by the local research team.

5.2.3.1 Principal investigator responsibilities to the participant

The participant must receive an information pack containing a PIL, a copy of the completed ICF, and a participant diary which has contact details for the local research team, and prompts for reporting of adverse events.

5.2.4 Consenting patients who lack capacity to consent themselves

We will actively facilitate inclusion of patients with dementia, cognitive impairment, or significant frailty as these are patients at high risk of odontoid fractures from low impact falls, and at high risk of complications from collar use. Excluding those without capacity would compromise the generalisability of the findings by recruitment of an unrepresentative study sample and would exclude this vulnerable population from the benefits of research evidence in improving practice.

The majority of patients found to have a new odontoid fracture will have an associated medical or trauma catastrophe (i.e. syncope/collapse/fall etc) associated with it. The pain, anxiety, effects of the acute environment and discomfort around initial collar management associated with the diagnosis and fracture will mean that most of these patients will not have capacity and may not have capacity to weigh up the pros and cons of the study for some time after the event. Therefore, we are seeking approval for including adults without capacity.

A personal or legal representative may provide consent for trial participation on the patient's behalf only if a patient lacks capacity to consent.

The consent procedures will adhere to the Adults with Incapacity (Scotland) Act 2000, the 2005 Mental Capacity Act and their accompanying Codes of Practice, and the Mental Capacity Act (Northern Ireland) 2016.[21,22] For patients in Scotland, who are assessed as lacking capacity to provide consent, we will ask the patient's nearest relative, welfare attorney or guardian to provide consent on the patient's behalf. For patients in England and Wales, and in Northern Ireland, who lack capacity to provide consent, we will seek advice of a personal consultee (relative or close friend) to take part. This consultee can provide advice or lack of known objection to the patient entering the study.

Consultee advice or consent will be written if possible. The consultee may be unable to visit the patient in hospital, because of families living long distances apart, if the spouse is frail or disabled, or because of (COVID-19) pandemic. We will therefore permit witnessed phone documentation of the consultee declaration (England, Wales, and Northern Ireland) or nearest relative consent (Scotland), with clear documentation of the discussion and named persons involved. All forms of consent/consultee documentation will be undertaken by trained team members on the delegation log, following adequate time for review of patient information and consent/consultee declaration forms, which can be posted or emailed to consultees where necessary.

A further consideration for patients lacking capacity is whether they can tolerate the standard care arm (collar). Patients with a fracture are usually put into a collar in the first instance as standard care and therefore will already have undergone a "trial of collar". If

they cannot tolerate or maintain the collar, then they will be excluded from randomisation as there is no option other than to treat their fracture without a collar.

The patient (or consultee, relative, next of kin, welfare attorney) can withdraw (the patient) from the study intervention at any time point without reason. Anonymised data prior to the point of complete withdrawal will be included for analysis. A clinician may also withdraw a patient from the trial if they feel this is in their best interest, including patients lacking capacity who fail to tolerate the collar after randomisation. Follow-up will continue unless the patient or their representative indicates otherwise. All available data will be included in an intention-to-treat analysis regardless of time-point of withdrawal from intervention.

5.2.4.1 Re-consenting patients who regain capacity

If a participant regains capacity during hospital stay, the participant should be made aware of their trial enrolment and full informed consent should be sought from the participant.

Once the patient has left hospital, there are no mandated face to face research assessments. A patient may however regain capacity after discharge. In participants who have not previously given their own consent to participate in this trial, we will send a cover letter at the time of each questionnaire to ascertain whether they have regained capacity to make considered decisions. We will include the patient information sheet and consent form relevant to participants who have regained capacity. If they can make considered decisions, then we will invite them to read the patient information sheet and to decide whether to continue in the trial.

All participants with mental capacity retain the right to withdraw consent at any time from trial participation.

5.2.4.2 Patients who have given consent but lose capacity

In Scotland, if a participant has already given written informed consent, but loses capacity, they will remain in the study. The initial consent for participation and continued completion of patient reported outcomes measures will be taken as ongoing willingness to participate. If they are unable to complete the study questionnaires their next of kin will be asked to complete them. The primary outcome questionnaire (EQ-5D-5L) is validated for proxy completion.

In the rest of the UK, if a participant has already given written informed consent, but loses capacity, they will remain in the study only if consent is then given by a consultee. If they are unable to complete the study questionnaires their next of kin will be asked to complete them. The primary outcome questionnaire (EQ-5D-5L) is validated for proxy completion.

5.2.5 New safety information

If the data monitoring committee suggests that the risk-benefit balance is significantly changed by any new safety information, the PIL and ICF will be reviewed and amended accordingly. Trial participants will be informed of the new information.

6 RANDOMISATION

6.1 RANDOMISATION PROCEDURE

Randomisation will be performed using a web-based randomisation system developed by the Edinburgh Clinical Trials Unit (ECTU). The patient will be assigned a study ID.

Randomisation algorithm
To avoid predictable treatment allocation and to minimise differences between the two arms of the trial, a minimisation algorithm will randomise patients based on three variables collected by research staff at baseline:

- Age at randomisation (<75 years versus 75 years or older)
- Odontoid Fracture type (I-III)
- Frailty (Rockwood score >4 versus 4 or less)

The minimisation algorithm will randomly allocate the first participant with a probability of 0.5 to one arm of the trial. Randomisation of subsequent participants involves adaptive stratification and allocates them with a probability of 0.8 to the group which minimises differences of variables listed above between the two arms of the trial.

6.2 AFTER RANDOMISATION

The local research team will inform the participant's GP about their patient's trial enrolment, treatment allocation, and the schedule of questionnaires.

6.3 TREATMENT ALLOCATION

Treatment allocation generated by the central randomisation service is disclosed to the local researcher at the point of randomisation via the web interface. The system will concurrently confirm treatment allocation by sending an email to the DENS Trial Team. The local research staff may access treatment allocation against the participant's unique study identification in the DENS secure website.

6.4 BLINDING

Treatment allocation is open to participants, treating clinicians, and the local research staff. Central research staff will conduct telephone follow-ups (6 and 12 months). Outcome event adjudication committee is blinded to treatment allocation.

7 PREMATURE WITHDRAWAL OF PARTICIPANTS

Participants are free to withdraw (or consultee, relative, next of kin, welfare attorney can withdraw a patient) from the study at any point, or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. We will request clarification of which part(s) of the trial that they wish to withdraw from. Data collected up to the point of withdrawal will be retained. Passive follow-up from their GP and secondary data sources will continue unless the participant withdraws from this.

8 CROSSOVERS

A decision to remove the hard collar earlier or later than 12 weeks in a patient allocated to standard care collar use may occur because of wishes from the participants, their

representative, or their doctor. Follow up in these patients will continue as per protocol and their data included in the primary analysis on an intention to treat basis according to the treatment allocation at randomisation. The date of collar removal and reason for timing of removal are recorded in the participant's CRF.

An insistence on a patient wearing a hard collar when allocated to early hard collar removal deviates from treatment allocation and may occur because of wishes from the participants, their representative, or their doctor. Follow up in these patients will continue as per protocol and their data included in the primary analysis on an intention to treat basis according to the treatment allocation at randomisation. The date of deviation and reason are recorded in the participant's CRF.

If a treatment change occurs because of a secondary outcome, or Serious Adverse Event (SAE), the event will be reported as per protocol (see below).

9 STUDY ASSESSMENTS

9.1 STUDY ASSESSMENTS

Study assessments are summarised in Table 1.

	Timing from Randomisation						
Assessment	Baseline	Hospital Discharge	2 weeks	6 weeks	12 weeks	6 months	12 months
Assessment of Eligibility Criteria	*						
Written informed consent	*						
Demographics							
Baseline data (as per 10.1)	*						
Rockwood clinical frailty score	*						
Imaging							
Odontoid Fracture Type	X						
Cervical Imaging (as per local policy)	X				X		
Outcomes							
EQ-5D-5L			*	*	*	*	*
EQ-VAS			*	*	*	*	*
NPRS			*	*	*	*	*
NDI			*	*	*	*	*
AEs and SAEs		*			*		
Late injury-related complications						*	*
Collar use		*	*	*	*		

Grip strength/bio-impedance	*				*		
service use			*	*	*	*	*
medication use			*	*	*		
mortality					*	*	*

Table 1: Timing of Study Assessments. Assessments undertaken as standard care are shown in red. Study specific assessments are shown in green. Assessments up to and including the 12 week assessment are recorded by the local research team. The 6 and 12 month assessments are recorded by the TCC, except for mortality (which is obtained by the local research team prior to TCC assessment).

9.1.1 Baseline data

Baseline study data (as per 10.1) will be recorded by the local research team.

9.1.2 Standard care follow-up

Standard care clinical follow-up is usually scheduled by the clinical team at approximately 2-weeks and 12-weeks post injury, but local protocols may vary. This can occur during initial admission if discharge is delayed, in an out-patient setting, or over the telephone, according to participating spinal unit standard care. The standard care follow-up will not be varied in patients allocated to early hard collar removal.

9.1.3 Research follow-up

This information will be collected from telephone interview, postal questionnaires, or online questionnaires (patient only), according to participant preference. If the research assessment is due when a participant is scheduled to attend hospital, the information may be collected face to face. Information may also be collected, or clarified, from the patient's medical notes. Where participants are unable to complete the assessment, their carer or designated representative will be asked to provide the information on their behalf. Whether the outcome measures are self-completed or completed by a carer or representative will be recorded.

The local research team will clarify that the participant has not died prior to each assessment being sent. The assessment should be undertaken on the target date from the time of randomisation, within the time windows as detailed in section 10.2. Where the questionnaire booklet which forms the basis of the assessment is mailed to the participant, it should be mailed to arrive within this window. Participants (or their relative/carer) will be asked to immediately complete the booklet and to return it in the pre-paid envelope. If a mailed questionnaire is not returned within 2 weeks of postage, up to 3 phone calls will be made to participants to aid full completion either by post or 'phone. If an online questionnaire is not completed within 2 weeks of being sent, up to 3 phone calls will be made to aid full completion either online or by 'phone. Unless they or their representative indicate that they wish to withdraw from the study, they will then be contacted again at the next study time-point.

9.2 LONG TERM FOLLOW UP ASSESSMENTS

Patients will be asked to consent to collection of outcome data and service utilization over 5 years (e.g. mortality, hospital admissions) using anonymized data through the Data SafeHaven.

10 DATA COLLECTION

10.1 BASELINE DATA

Baseline data will be recorded by a member of the local research team as soon after randomisation as possible. This will include:

- Patient characteristics: age, sex, Rockwood clinical frailty score
- Scottish, Welsh or English Index of Deprivation - Social quintile based on post code
- Comorbidities
- Prescribed and non-prescribed drugs (Anonymised data from electronic prescribing system or manually recorded)
- Acute conditions contributing to fall (e.g., urinary, or respiratory tract infection)
- Assessment of Glasgow Coma Scale on admission to hospital
- Assessment of peripheral dermatomes and myotomes (standard neurological examination of arm and leg sensation and power).
- Trauma characteristics: mechanism of injury, timing of injury,
- Fracture characteristics: Anderson & D'Alonzo fracture type, fragment displacement, fragment angulation, canal narrowing
- Additional non-cervical injuries related to fall
- Any additional imaging abnormalities relating to trauma/fall
- Admission haemoglobin, albumin, CRP, where assessed as part of standard care
- Initial treatment: whether immobilised, time point at which immobilised, mechanisms of immobilisation, analgesia given
- Domicile at time of admission
- Grip Strength and bioimpedance (where available)

Quality of life assessment tools are not employed at the baseline assessment.

Follow-up data collected on discharge;

- Date of removal of hard collar in patients allocated to early removal
- Length of hospital stay
- Discharge destination / change in discharge destination from admission
- Analgesia used during admission
- Discharge social care package

10.2 RESEARCH FOLLOW-UP

Participants will be asked to keep a diary for 12 weeks from the time of randomisation as to whether they need any pain killers (for any indication) each day. If they are allocated to wearing a collar then they will also record when they are wearing it each day. They will be provided with an envelope to return the diary to their local research team for entry into the research database.

Research assessments will be carried out at 2 weeks (+/- 1 week), 6 weeks (+/- 2 weeks), 12 weeks (+/-2 weeks), 6 months (+/- 4 weeks) and 12 months (+/- 4 weeks) post-randomisation.

2 week, 6 week and 12-week assessments will be undertaken by the local research team. They are questionnaire based and will be administered by mail, telephone, or online (patient only). Assessment may take place in combination with any standard clinical review.

6 month and 12 month questionnaire assessments will be coordinated by the trial coordinating centre and will be administered by mail, telephone, or online. Prior to the 6 and 12 month assessments the local research team will confirm that the participant is still alive and indicate this in the trial database. Details of healthcare service use will be collected from the patient questionnaires.

Where a questionnaire is not returned within one week of being sent, the patient will be contacted by the local trial team (2, 6 and 12 weeks) or the central trial team (6 and 12 months) by telephone or email, up to three times.

The following data will be collected:

- Outcome measures including EQ-5D-5L, and NDI.
- Regular analgesic medication as per medication diary or combined collar and medication diary, according to treatment arm
- For participants in the standard treatment (collar) arm, reported collar use in combined collar and medication diary, and date of removal
- Primary care visits
- Other service use (including physiotherapy, occupational therapy, district nursing)
- Repeat hospitalisations including ambulance use, Emergency Department visits, outpatient and inpatient attendance/stays
- Adverse events that have occurred since last follow-up, up to 12 weeks
- Mortality at 3, 6 and 12 months
- Grip Strength and bioimpedance (where available) at 12 weeks

Late injury-related complications, such as new neurological deficit will be assessed during the 6 month and 12-month follow-up questionnaire.

- New or progressive neurological deficits
- Chronic swallowing problems

The results of any cervical spine imaging performed since the last research review will be recorded. Evidence of bony healing, fracture displacement, fracture angulation, canal narrowing, and changes from baseline, as reported by the radiologist, will be documented.

In participating units where facilities are available to measure bioimpedance and grip strength, consecutive randomised patients will be invited to undergo these assessments. These are used as objective assessments of frailty to support interpretation of the clinical stratification by Rockwood Clinical Frailty Score.

We will ask for patient consent for review of imaging by the study team. All identifiable images will be stored and transferred within the NHS PACS network. Where this is not possible, only anonymised scans will be processed outside the NHS PACS network. Anonymised imaging data will be labelled only with the study number and stored on

anonymised CDs or on encrypted hard drives and processed using computers with limited access via usernames and passwords.

Where participants are unable to complete the assessment, their carer or designated representative will be asked to provide the information on their behalf. Whether the outcome measures are self-completed or completed by a carer or representative will be recorded.

10.3 SOURCE DATA DOCUMENTATION

Data will be inputted by the local research team (baseline, 2 week, 6 week, 12 week assessments, and mortality at 6 and 12 months) or TCC with the local EMERGE research team (6 and 12 month assessment) directly into the online electronic database or will be collected on case report forms and paper questionnaire proformas before being entered into the electronic database. Where available patients will be able to complete patient reported outcome measures directly online.

11 DATA MANAGEMENT

11.1 PERSONAL DATA

The following personal data will be collected as part of the research:

- Patient name, address, telephone, contact email, and patient representative details, will be recorded on a contact details CRF and stored securely within the ECTU study database to facilitate central follow up by the research team at each site. Access to contact details data will be minimised and only accessible to those with delegated responsibility. This includes members of the central trial team and NHS Lothian EMERGE research team. Personal data will be stored securely for a minimum of 5 years after the study end date
- National Health Service (NHS) number, hospital number, Community Health Index (CHI) number, or other unique hospital identifier will be recorded by the local research team, alongside the unique study identification number allocated at randomisation. Only the unique study identification number will be recorded in the electronic database.
- In patients who consent to 5 year data linkage follow-up, their National Health Service (NHS) number, hospital number, Community Health Index (CHI) number, or other unique hospital identifier will be shared with the CTT by secure NHS email. This will be stored securely on a NHS computer by the CTT, with the study ID, separate from any other patient data. It will be used for data linkage through the data Safe Haven.
- Consent forms will be stored securely in a locked office.
- Sex

Personal data will be stored by each local research team in a secure location according to local NHS/University policies, as applicable. Paper copies will be filed in a locked drawer with limited numbers of staff with access. Electronic study documents will be stored on a specially designated password protected drive/computer with password protected database on a shared drive with limited access.

Baseline and follow up data to 12 weeks will be collected by the local research team at each site. Data sources include the patient's clinical notes, radiology reports, and through

interaction with the patient as part of clinical care, or through interaction with other staff members caring for the patient. Data will be entered anonymously into a study specific secure database using the participant's unique study number. The local research team can only view the records of patients from their own centre.

Data generated from the i-button temperature sensors is anonymised at source using a numerical code intrinsic to the device. This numerical code will be recorded on the electronic database. The anonymised data from each i-button will be collected by the central trial team.

Access to collated participant data will be restricted to individuals from the research team treating the participants and representatives of the sponsor. Computers used to collate the data will have limited access measures via usernames and passwords. Published results will not contain any personal data that could allow identification of individual participants. All evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access.

11.2 STUDY DATABASE

The study database will be created and maintained by ECTU. The database will be compliant with the relevant regulations and sponsor Standard Operating Procedures (SOPs). Trained and delegated members of the research team will be given password protected logins to the database. The data will be stored on a secure server in the University of Edinburgh.

11.3 ARCHIVING OF SITE DATA

All trial related and source documents should be archived for five years in accordance with the Sponsor's archiving policy.

11.4 ARCHIVING OF CENTRAL DATA

All trial related documents will be archived for five years in accordance with the Sponsor's archiving policy unless an alternative longer archiving period is specified by the sponsor or the funder. The TSC will have access to the final trial dataset and will consider applications to access the dataset by investigators or others, subject to a data sharing agreement.

11.5 DATA CONTROLLER

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws.

11.6 DATA BREACHES

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

12 STATISTICS AND DATA ANALYSIS

12.1 SAMPLE SIZE CALCULATION

12.1.1 Main Study

The study will recruit a target of 887 participants from an anticipated 25 sites recruiting for between a minimum of 23 months and a maximum of 30 months (with staggered recruitment of 2 sites per month for calendar month 6 to 20) at an average of 1.63 per site per month (assuming sites can recruit on average 11 months out of 12 to allow for holidays).

The justification is given as follows:

The minimum clinically important difference underlying our calculations is 0.05. The study has 90% power and a 5% level of significance. The standard deviation of EQ-5D-5L at 12 weeks (the primary outcome) is assumed constant between the two randomised groups and not more than 0.30.

The correlation between the baseline covariates and 12-week EQ 5D-5L is complicated by not having a baseline measurement of EQ-5D-5L, which often is the highest correlate of the primary outcome. It is not possible to measure a meaningful baseline EQ-5D-5L in this context, because this is not recorded prior to injury and the QoL on immediate hospital admission will be influenced by the injury. Instead, a profile of baseline covariates (age, Rockwood clinical frailty scale) will be used. We are anticipating that the overall correlation of these baseline factors and 12-week EQ-5D-5L, through a linear model, will be around 0.5, which will secure a 25% reduction in sample size. The higher the correlation, the larger the reduction in sample size. For the serial correlation of the post-randomisation measures of EQ-5D-5L at 2, 6 and 12 weeks, we assume a serial correlation of 0.44 (here, the lower the correlation, the higher the reduction in sample size) then we achieve a 37.5% reduction in sample size.[23] We intend to run simulations to better quantify the actual observed correlation structure and what this then means for the sample size re-estimation step.

In terms of the proportion of missing data, we have initially set this at 20%, given the age of the participants, and that the primary outcome is a health questionnaire, but also reflecting the short follow-up. This is based on experience of several trials using EQ-5D across many areas. By using evidence-based strategies for retention we hope to reduce this attrition rate.

Putting all of this together, we calculate, unadjusted, that at 90% power and 5% level of significance, using a two-sided two-sample t-test, for an effect size of 0.05/0.30 or 1/6 we would need a total of 1514 patients. Allowing for 20% missing data increases that to 1514/0.8=1893. Reducing this by 25% for baseline correlation takes this to 1419. Reducing this by 37.5% for serial correlation takes this to **887 to be randomised**, roughly 1:1, in total.

A preliminary TARN (Trauma Audit and Research Network) database search identified an annual incidence of at least 1,700 odontoid fractures, 85% of which were in people aged over 65 years. To get a more precise assessment of the actual number of older and frail patients with an odontoid fracture available for recruitment, we manually searched acute referral and fracture clinic out-patient records. We identified on average 4-5 patient referrals per month with odontoid fractures at 2 neurosurgical units (Plymouth, Edinburgh). These patients were managed in a collar. Review against study eligibility criteria indicated at least half of these patients would be eligible for our study. Based on a comparison of the referral populations for Edinburgh and Plymouth with other spinal units and, with an achievable recruitment of 50% of eligible patients, we estimate being able to recruit an average of 2 patients per unit per month. Twenty-five spinal units in the UK have already indicated support for the study.

12.2 PROPOSED ANALYSES

12.2.1 Primary Analysis

A detailed statistical analysis plan (SAP) will be developed by the study statisticians and finalised prior to the locking of the trial database in consultation with the independent study oversight committees.

Throughout, a 5% two-sided significance level will be used. The intention to treat principle will be followed in the primary analysis.

Analysis of the primary outcome (EQ-5D-5L at 12 weeks) will be a repeated measures analysis of covariance, including terms for treatment (collar versus no collar) and the EQ-5D-5L responses at 2, 6 and 12 weeks. Adjustments will be made for the variables included in the randomisation minimisation algorithm - age (<75 versus ≥75), odontoid fracture type (I-III), Rockwood clinical frailty scale (>4 versus ≤4). Adjustment for study site will be included (as a random effect), if appropriate. This repeated measures approach enables the estimation of an intervention effect at week 12 (primary outcome), while also allowing for an overall assessment of the effect of intervention over the 12-week outcome period.

Neck Disability Index (NDI) will be considered as the most important secondary outcome. The 12 week NDI will be analysed in line with the primary analysis of EQ-5D-5L at 12 weeks. It is anticipated that results of this analysis will underpin any differences seen in EQ-5D-5L between the groups, thus confirming and strengthening the clinical interpretation of these findings. All other secondary outcomes will be analysed with statistical models appropriate to the distribution of the outcome (e.g. linear, logistic or count). Where there are data recorded on multiple occasions post randomisation (2, 6 and 12 weeks, 6 and 12 months) we may use an appropriate repeated measures model, in line with the methods described for the primary analysis.

All types of odontoid fracture (I-III) will be analysed together in the primary outcome. An exploratory subgroup analysis by fracture type will be performed. An exploratory frailty sub-group analysis of the primary outcome will also be conducted where frailty is defined as a frailty score >4. Additional subgroup analyses will consider age (<75 versus ≥ 75 years).

The influence of any missing data on the robustness of the findings will be examined e.g. using multiple imputation models under a missing at random assumption. Details will be provided in the Statistical Analysis Plan.

12.2.1.1 Measurement of Costs and Outcomes

The analysis in this subsection will be undertaken by the health economics' team.

A 12 month within trial analysis will be undertaken based on NICE reference case recommendations to maximise UK policy relevance.[24] This will include: Adoption of an NHS and Personal Social Services (PSS) decision perspective; cost-utility approach for primary analysis (results presented in terms of incremental cost per quality adjusted life year (QALY) derived from EQ-5D-5L data with an area under the curve approach, omitting baseline); discount rate of 3.5% for both costs and QALYs (where applicable); and use of probabilistic sensitivity analysis (PSA), to generate cost effectiveness acceptability curves (CEACs).[24] Choice of primary analysis cost per QALY threshold and EQ-5D-5L scoring algorithm will be

selected to match NICE preferences at time of data lock. NHS & PSS resource use (collars/pads, district nurse visits, social care, initial inpatient care and readmissions, ambulance trips, A&E, physiotherapy, imaging, other outpatient and primary care visits will be extracted from medical records where possible, with some top-up self-report surveying. These will be combined with standard UK price weights[25,26] to generate costs. Consent for long term follow up will include permission to access medical records to enable any future secondary reuses of the data to include NHS resource use.

Missing data will be imputed using appropriate techniques depending on degree of missingness, likely multiple imputation by chained equations (which is considered gold standard in this area). Though we note that most important cost factors such as inpatient readmission and home care packages will be obtained from medical records and EQ-5D up to 12 weeks (where we expect greatest difference), which will be researcher administered.

12.2.2 Interim Analyses

12.2.2.1 Recruitment internal pilot

To ensure the study is feasible in terms of recruitment, the first internal recruitment pilot will be undertaken from 18 centres to recruit 132 (15% total) patients in 9 months. Among the 132 patients randomised, around 60 are expected to have full 12-week data. To progress to the full trial, we will observe the stop-go rules below:

- Feasibility of recruitment will be assessed with a target of 132 patients (15%) in 9 months, recruitment rate/site/month of 1.63, more than 10 sites open and adherence failure less than or equal to 10% (Table 2).
- Adherence is based on the proportion of recruited patients who either withdraw from the study or 'cross-over' between the treatment arms. 'Cross-over' includes those randomised to a collar who do not wear it, and those randomised to no collar where the clinician insists that they continue to wear a collar.
- Green = continue unchanged; Amber = make changes, including more sites and/or longer time to recruit; Red = consider stopping as study considered not feasible, unless identifiable and rectifiable cause.
- All the criteria need to be met to achieve a Green assessment.
- Independent data monitoring committee approval to continue without evidence of harm in one group.

	Red	**Amber**	**Green**
Total number of participants recruited	≤108	109-131	≥132
% Threshold of recruitment	≤82%	83%-99%	100%
Recruitment rate/site/month	1.07	1.33	1.63
Number of sites open	<5	5-10	>10
Adherence failure	>20%	11-20%	≤10%

Table 2: study progression criteria

12.2.3 Sample size re-estimation pilot

In addition to the stop-go pilot for recruitment we will conduct a second, longer internal pilot to assess whether sample size re-estimation is necessary. We will prepare a report for the Trial Steering Committee on blinded data,[27,28] using a simulation approach based on mature data for the 12 week outcome from the first 300 randomised participants. We consider this to be prudent given the uncertainty in the assumptions around variability (the standard deviation), the magnitude of the two types of correlation (baseline factors with 12 week EQ-5D-5L; and serial correlation between on-treatment repeated measures of EQ-5D-5L) and the percentage of missing data. We expect that since we have tended to make conservative assumptions about the influencing parameters, particularly the assumed standard deviation, there will only be a small probability that the sample size will need to be increased, and a much larger probability that the sample size can actually be reduced.

12.2.4 Qualitative study Data analysis

Data will be analysed thematically using the method of constant comparison. Data analysis will also be informed by relevant epistemologies; these will be identified through immersion in the literature prior to data collection as well as a result of emerging findings. To ensure rigour, several individuals will be involved in data analysis and coding. We will also seek input from our study interactive working group to clarify and confirm our interpretations of the data.

12.2.5 Health Economics

The Health Economics analysis will be led by the Edinburgh Clinical Trials Unit team.

A 12 month within trial analysis will be undertaken based on NICE reference case recommendations to maximise UK policy relevance.[24] This will include: Adoption of an NHS and PSS decision perspective; cost-utility approach for primary analysis (results presented in terms of incremental cost per quality adjusted life year (QALY) derived from EQ-5D-5L data with an area under the curve approach, omitting baseline); discount rate of 3.5% for both costs and QALYs (where applicable); and use of probabilistic sensitivity analysis (PSA), to generate cost effectiveness acceptability curves (CEACs).[24] Choice of primary analysis cost per QALY threshold and EQ-5D-5L scoring algorithm will be selected to match NICE preferences at time of data lock.

NHS & PSS resource use (collars/pads, district nurse visits, social care, initial inpatient care and readmissions, ambulance trips, A&E, physiotherapy, imaging, other outpatient and primary care visits) will be extracted from medical records where possible, with some top-up self-report surveying. will be combined with standard UK price weights[25,26] published at the time to generate costs. The latest financial year for which at least one study participant provides data, and prices are available will be selected as base year. Costs will be grouped and summed into four categories: (1) Direct intervention costs; (2) Primary care (including prescribing); (3) secondary care; and (4) social care. Total costs will be the sum of these four factors.

Univariate mean QALYs, Resource use, and Costs (by group and total) will be presented for each trial arm alongside differences in means (intervention minus control), and associated 95% confidence intervals. Multivariate analysis of both QALYs and Total costs, will also be presented controlling for baseline costs where available, and minimisation variables. It is not

possible to control for baseline utility as it is not possible to collect this. PSA will be undertaken using the recycled predictions technique[29], with results presented in in scatter plots with percentage probabilities of cost-effectiveness reported for £20,000 and £30,000 per QALY as per NICE reference case requirements[24], and varied over wider ranges via CEAC.

Missing data will be imputed using appropriate techniques depending on degree of missingness, likely multiple imputation by chained equations (which is considered gold standard in this area). Though we note that most important cost factors such as inpatient readmission and home care packages will be obtained from medical records and EQ-5D up to 12weeks (where we expect greatest difference) will be researcher administered.

13 ADVERSE EVENTS

It is the responsibility of the Principal Investigator to detect and document events meeting the criteria of adverse events. The PI may delegate this role to a suitably qualified physician in the research team who has an up-to-date Good Clinical Practice training. AEs will be recorded in the electronic Case Report Form (eCRF) or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

Assessment for AEs will be made by a clinical member of the research team on discharge from hospital, any re-admissions to hospital and at the 12-week follow-up. After this time point AEs will no longer be collected.

13.1 DEFINITIONS

13.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with the allocated trial intervention.

13.1.2 Serious adverse event

A serious adverse event (SAE) is any AE that:

- Results in death
- Is life threatening i.e. the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Results in any other significant medical event not meeting the criteria above e.g. may jeopardise the participant or may require intervention to prevent one of the other listed criteria

13.1.3 Disease-specific adverse events (DSAE)

There are some specific adverse events related to the fracture and collar care that we would like to ensure we capture during follow-up time points up to 12 weeks. Therefore the patients and/or representatives will be prompted to assess whether these have occurred

during each follow-up. If there is any concern that a reported DSAE is serious then the patient will be contacted directly to assess further.

Short-term DSAEs will be assessed by the local research team at discharge, and by questionnaire at 2-weeks, 6-weeks, 12-weeks, including;

- Collar sores and/or skin alterations/redness
- Dysphagia (difficulty swallowing) and/or difficulty eating/drinking
- Falls and unsteadiness

These will be added to the AE log but not reported to the sponsor.

14 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

14.1 PRE-EXISTING MEDICAL CONDITIONS

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

14.2 WORSENING OF THE UNDERLYING CONDITION DURING THE TRIAL

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

14.3 ASSESSMENT OF AES AND SAES

Each AE must be assessed for seriousness, causality, severity and unexpected SAEs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.

14.3.1 Assessment of Seriousness

The PI or delegated physician will assess seriousness as defined in Section 13.1.2.

14.3.2 Assessment of Causality

The PI or delegated physician will assess whether the AE or SAE is likely to be related to the study hard collar allocation (collar or no collar):

- Unrelated: where an event is not considered to be related to the study hard collar allocation

- Possibly related: the nature of the event, the underlying medical condition, concomitant medication, or temporal relationship make it possible that the AE has a causal relationship to the study hard collar allocation

Alternative causes such as natural history of the underlying disease, other risk factors and temporal relationship of the event to the treatment should be considered and investigated. Where there are two assessments of an AE, for example, the PI and the CI, the assessment made by the PI cannot be downgraded, but the CI can upgrade an event. In the case of a difference of opinion, both assessments are recorded and the 'worst case' assessment is used for reporting purposes.

14.3.3 Assessment of Expectedness

If the event is an SAE that is possibly related to the intervention the evaluation of expectedness will be made based on knowledge of the intervention

The event may be classed as either:

Expected: the SAE is consistent with the intervention.

Unexpected: the SAE is not consistent with the intervention.

14.3.4 Assessment of Severity

The PI or delegated physician will assess the severity for each SAE and record this on the CRF or AE form according to one of the following categories:

- *Mild*: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities
- *Moderate*: an event that is sufficiently discomforting to interfere with normal everyday activities
- *Severe*: an event that prevents normal everyday activities. The term 'severe' should not be confused with 'serious', which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

14.3.5 Expected complications of odontoid fracture and hard collar use

The hard collar is expected to be associated with the following complications:

- Collar sores and/or skin alterations/redness
- Dysphagia and/or difficulty eating/drinking
- Recurrent Falls
- Poor balance

These will be documented on the AE log but not reported to the sponsor

14.4 DETECTING ADVERSE EVENTS

All outcomes and AEs will be sought from the time a participant signs the consent form to take part in the study until 12 weeks, using follow-up methods as described above.

14.5 REPORTING ADVERSE EVENTS

If a PI or delegated physician becomes aware of an AE, it is their responsibility to review all documentation related to the event. Information collection includes type of event, onset date, PI assessment of severity and causality, date of resolution as well as treatment required, investigation needed and outcome. If the AE is detected by central means of follow-up, the local research team will initiate the collection of this information, but enlist the help of local personnel to acquire relevant clinical information. These data will be presented to the DMC.

Initial reporting of reportable adverse events should be done using the electronic form on the trial website. If the event is serious, it should be reported to ACCORD within 24 hours using the sponsor CR006 form

The investigator must report SAEs to the sponsor within 24 hours of becoming aware of the event. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

PIs need not report to the TCC or sponsor any non-fatal AEs that are not SAEs. These will be captured on the AE log.

SAE reports will be emailed as a PDF file to Safety@accord.scot

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner. All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

14.6 SAES FOLLOW-UP

After recording and reporting safety events, it is the responsibility of the PI to follow up the affected participant(s) until resolution of the event or death of the participant(s). If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

If the outcome of an initial report of an event is one of the following outcome options:

- Condition still present and unchanged
- Condition deteriorated
- Condition improving

Then the investigator must follow up with the participant(s). A safety report will not be considered complete until the outcome is:

- Completely recovered (including date of recovery)
- Recovered with sequelae (including date of recovery)
- Death (including date of death)

14.7 REPORTING REQUIREMENTS

ACCORD has a legal responsibility to notify the relevant ethics committee (Research Ethics Committee (REC) that approved the trial of any unexpected and possibly related SAEs. These will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all unexpected and possibly related SAEs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance.

15 OVERSIGHT ARRANGEMENTS

The trial funder (NIHR) and co-sponsors (University of Edinburgh and NHS Lothian) did not influence trial design. The sponsor ensures that data collection, management and trial monitoring are conducted appropriately and has overall responsibility for the study. Neither the funder nor the sponsor will have ultimate authority over writing of the report or the decision to submit the report for publication.

15.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by the Trial Management Group based at the Edinburgh Clinical Trials Unit (ECTU) (Appendix 1), consisting of the Chief Investigator, the Trial Manager, Trial Statistician and other project staff. The TMG will oversee the study and will be accountable to the Chief Investigator. This group will meet regularly.

15.2 TRIAL COORDINATING CENTRE

The TCC is responsible for all aspects of the management of DENS and is based at ECTU. Responsibilities are stated within the co-sponsorship document and include regulatory submissions and compliance; financial management; monitoring of sites; training, patient information and communication; outcome assessment; data collection systems and data management; statistical analysis; reports and publications and archiving of the TMF in accordance with funder and sponsor requirements. Documentation will follow sponsor SOPs.

15.3 TRIAL STEERING COMMITTEE

The TSC oversees the conduct and progress of the trial (Appendix 1). A statement of their competing interests is available on request.

15.4 DATA MONITORING COMMITTEE

The DMC (Appendix 1), which is independent of the sponsor, oversees the safety of participants in the trial, according to the terms of reference in the DMC Charter, which is available from the TCC, and the Sponsor SOP.

15.5 INSPECTION OF RECORDS

Research staff and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsors and REC review. In the event of an audit or monitoring, the PI agrees to allow the representatives of the sponsor direct access to all study records and source documentation.

15.6 STUDY MONITORING AND AUDIT

The trial will routinely collect data on outcomes, AEs and SAEs, and these will be reviewed by the independent DMC. The trial procedures are based on a routine clinical procedure (application of a hard cervical collar); collecting routine clinical information from the medical records; and informed consent. There are no complex procedures or interventions for the participants or research staff in this trial. Clinical management for underlying conditions will remain as per each hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in this research study is low. The study internal monitoring procedure to assure

appropriate conduct of the trial will use a combination of central data monitoring and remote self-monitoring unless issues are identified that can only be addressed by site monitoring. This will be regularly reviewed during the trial.

15.6.1 Archiving of site data

All trial related and source documents should be archived for five years in accordance with the Sponsor's archiving policy unless an alternative longer archiving period is specified by the sponsor or the funder. The costs for this must be discussed and agreed locally by each research and development (R&D) department as part of the R&D approval process.

15.6.2 Archiving of central data

All trial related documents will be archived for five years in accordance with the Sponsor's archiving policy unless an alternative longer archiving period is specified by the sponsor or the funder. The TSC will have access to the final trial dataset and will consider applications to access the dataset by investigators or others.

15.7 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

16 GOOD CLINICAL PRACTICE

16.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP).
Before the study can commence, all required approvals will be obtained, and any conditions of approvals will be met.

16.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

16.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the PI or qualified delegated person and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given enough time to consider the information provided. It should be emphasized that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

16.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

16.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

16.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs, according to SOP.

16.2.5 GCP Training

All researchers are encouraged to undertake GCP training in order to understand the principles of GCP. GCP training status for all investigators should be indicated in their respective CVs.

16.2.6 Confidentiality

All evaluation forms, reports, and other records will be identified using the unique study identification number allocated at randomization to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

16.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data

Protection Regulation and Data Protection Act 2018) about the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via usernames and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified, and re-identification is not likely to take place

17 STUDY CONDUCT RESPONSIBILITIES

17.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator. Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

17.2 MANAGEMENT OF PROTOCOL NON-COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

17.3 SERIOUS BREACH REQUIREMENTS

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 participants of the trial; or
(b) The scientific value of the trial.
If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

17.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

17.5 END OF STUDY

The end of study is defined as the last participant's last follow up assessment at 12 months following recruitment. Data linkage will be used to collect five year outcome data in consenting patients. No further patient involvement will be required after their final assessment at 12 months.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

17.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

There is no intervention that continues beyond the end of the study.

17.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

18 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

18.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

The primary trial publication will be drafted by a writing committee. The co-authors of publication(s) connected to this trial will reflect the people who have made a major contribution to developing, implementing, and conducting the study, analysing and interpreting the data, and preparing the manuscript. Principal investigators and those included in the Delegation Logs for patient recruitment will be invited to be in the collaborator list that will be included with the principal publication reporting the outcome of the study.

18.2 PUBLICATION

The results will be published in a leading peer reviewed journal and presented at national and international meetings

At the end of the study, we will produce a plain language summary of the results of the study, and a visual abstract.

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