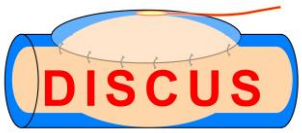

FULL/LONG TITLE OF THE STUDY	**D**uroplasty for **I**njured cervical **S**pinal **C**ord with **U**ncontrolled **S**welling
SHORT STUDY TITLE / ACRONYM	DISCUS
PROTOCOL VERSION NUMBER AND DATE	V10.0 05Dec2025
Study Type / Phase:	III
IRAS Number:	292031 (England, Wales, Northern Ireland- EWN) (Scotland ONLY 296518-S)
EudraCT Number	N/A
Clinical Studies registry number (ISRCTN Number / Clinical trials.gov Number):	ISRCTN: 25573423 Clinicaltrials.gov Number: NCT04936620
NIHR CRN CPMS	48627
Funder (EME, an MRC and NIHR partnership)	NIHR130048
City St George's University London, JRES (sponsor) Reference Number	2021-0056
This protocol has regard for the HRA guidance and order of content	

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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

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

For and on behalf of the Trial Sponsor:

Signature: Date: 18/12/25

.....

Name (please print):

GHAZAL EBRAT

.....

Position:

Research Governance and Facilitation Officer

.....

Chief Investigators:

Signature: Date: 5 DEC 25

.....

.....

Name: (please print):

MARIOS PAPADOPOULOS .....

SAMIRA SAADOUN .....

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Funder(s)	Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership (Project No. NIHR130048)
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Committees	**Trial Management Group**: Membership will consist of personnel involved in daily operational issues in the management of the trial and will act upon advice/recommendations received by the Sponsor and/or the Data Monitoring Committee. The DISCUS TMG will consist of the following: 1. The trial manager (Chair) 2. Chief Investigator and Co-Chief Investigator 3. An OCTRU statistician 4. The PPI co-applicant Other key members of the scientific/clinical team and, where necessary, the Lead Statistician and SITU Operational Lead. **Trial Steering Committee**: Membership will consist of personnel directly involved in the trial and/or independent individuals. The TSC will concentrate on the progress of the trial in relation to protocol compliance and review of any participant safety considerations including the review of any recommendations made by the Data Monitoring Committee if relevant to the trial and to advise the sponsor and/or CI and Co-CI of any decisions. The DISCUS TSC will consist of the following: 1. CHAIR: Mr. Kismet Hossain-Ibrahim, Consultant Neurosurgeon, Ninewells Hospital, Dundee, NHS Tayside & University of Dundee 2. Trish Hepburn, Senior Medical Statistician, Nottingham Clinical Trials Unit, University of Nottingham 3. Dr Rupert Earl, patient body member, ex-patient and ex-chair of spinal Injuries Association (SIA) 4. Mr. Naveen Kumar, Consultant in spinal injuries, Chair of British Association of Spinal Cord Injuries Specialists (BASCIS), The Robert Jones & Agnes Hunt Orthopaedic Hospital 5. Marios C. Papadopoulos (co-CI) Invited observers include: 1. Representative of Sponsor (City St George's JRES). 2. Funder representative 3. Samira Saadoun (co-CI) 4. Sophie Reynolds (Trial manager)

	Data and Safety Monitoring Committee: The DSMC is an independent committee established to assess at intervals the progress of the clinical trial, the safety data and the critical efficacy end-points; and to recommend to the Trial Steering Committee whether to continue, modify or stop the trial. 1. CHAIR: Mr. Ahmed Toma, Consultant Neurosurgeon and Honorary Associate Professor, National Hospital for Neurology and Neurosurgery, London 2. Mr. Sorin Bucur, Consultant Neurosurgeon, University Hospitals Sussex NHS Foundation Trust 3. Dr. Kelly Handley, Senior Medical Statistician, Birmingham Clinical Trials Unit, University of Birmingham
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Statistician	Lead Statistician: Dr Daphne Kounali, email: daphne.kounali@ndorms.ox.ac.uk Trial statistician: OCTRU Statistician, Oxford Clinical Trials Research Unit (OCTRU), Centre for Statistics in Medicine (CSM), Nuffield Department of Orthopaedics, University of Oxford, Botnar Research Centre, Oxford, OX3 7LD, email: octru-stats@ndorms.ox.ac.uk
Trials Pharmacist	N/A
International Sponsor	Gemeinnützige Salzburger Landeskliniken Betriebsgesellschaft mbH (SALK) Müllner Hauptstraße 48, 5020 Salzburg, Austria

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ii. LIST OF ABBREVIATIONS

AE	Adverse Events
AIS	American spinal injuries association Impairment Scale
AMS	AIS Motor Score
APR	Annual Progress Report
AR	Adverse Reaction
BASCIS	British Association of Spinal Cord Injury Specialists
CI	Chief Investigator
CNS	Central Nervous System
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
CRN	Clinical Research Network
CSF	Cerebro-Spinal Fluid
CT	Computed Tomography
CUE-Q	Capabilities of Upper Extremity Questionnaire
ΔAIS-MS	Change in AIS motor score
DMP	Data Management Plan
DISCUS	Duroplasty for Injured cervical Spinal Cord with Uncontrolled Swelling
DSMC	Data and Safety Monitoring Committee
ELISA	Enzyme Linked Immuno Sorbent Assay
EMSCI	European MultiCentre Study of Human Spinal Cord Injury
EME	Efficacy and Mechanism Evaluation
EU	European Union
eTMF	Electronic Trial Master File
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEE	Generalised Estimating Equations
GROα	Growth Related Oncogene alpha
HRA	Health Research Authority
HES	Hospital Episode Statistics
HRQoL	Health Related Quality of Life
ICU	Intensive Care Unit
IEP	Image Exchange Portal
IHP	Independent Health Professional
ISCoPE	Injured Spinal Cord Pressure Evaluation
IL10	Interleukin 10
IL1α	Interleukin 1 alpha
IL1β	Interleukin 1 beta
IL4	Interleukin 4
IL8	Interleukin 8
IP10	Interferon gamma-induced protein 10
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
ISP	Intra Spinal Pressure
ISF	Investigator Site File
JRES	Joint Research and Enterprise Services

LPR	Lactate-to-Pyruvate Ratio
MCP1	Monocyte Chemoattractant Protein 1
MD	Microdialysis
MIP1α	Macrophage Inflammatory Protein 1 alpha
MIP1β	Macrophage Inflammatory Protein 1 beta
MMRM	Mixed Models for Repeated Measures
MRI	Magnetic Resonance Imaging
MTC	Major Trauma Centre
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Clinical Excellence
NICU	Neuro Intensive Care Unit
NIHR	National Institute of Health Research
NIMP	Non-Investigational Medicinal Product
OCTRU	Oxford Clinical Trials Research Unit
OS	Overall Survival
PACS	Patient Archiving and Communication System
PI	Principal Investigator
PIS	Participant Information Sheet
PPE	Personal Protective Equipment
PPI	Patient Public Involvement
QRI	QuinteT Recruitment Intervention
RCT	Randomised Control Trial
REC	Research Ethics Committee
RESCUEicp	Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure
RISCIS	Riluzole in Spinal Cord Injury Study
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCIM-III	Spinal Cord Injury Independence Measure (version III)
SCPP	Spinal Cord Perfusion Pressure
SDV	Source Data Verification
SF-36	Short Form 36
SIA	Spinal Injuries Association
SITU	Surgical and Interventional Trials Unit
SOP	Standard Operating Procedure
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSCI	Traumatic Spinal Cord Injury
WISCI-II	Walking Index for Spinal Cord Injury (version II)

iii. TRIAL SUMMARY	
Trial Title – Full and short	Duroplasty for Injured Cervical Spinal Cord with Uncontrolled Swelling, DISCUS
Clinical Phase	Phase III randomised controlled trial
Trial Design	Randomised, controlled, double-blind, multi-centre, superiority
Trial Participant Population	Acute, severe, traumatic spinal cord injuries (TSCI)
Eligibility Criteria:	**Inclusion:** 1. Age ≥16 years; 2. Severe cervical (C2 – T1) TSCI (AIS grade A–C); 3. Deemed to require and be suitable for surgery that includes laminectomy by local surgeon; 4. Surgery within 72 hours of TSCI; 5. Able to provide informed consent (except in emergency) or consultee declaration or nearest relative/guardian or welfare attorney (proxy consent).
	Exclusion: 1. Probable dural tear due to TSCI; 2. Life-limiting or rehabilitation-restricting co-morbidities; 3. Thoracic or lumbar TSCI; 4. Other central nervous system (CNS) disease
Planned Sample Size/Target	For UK recruitment only, the planned sample size is N=222 (85% power, 95% significance level). The planned sample size target may be increased to N=260 (90% power, 95% significance) depending on recruitment rate from international sites.
Treatment duration	10 – 15 minutes (to perform expansion duroplasty) 5 – 10 minutes (to insert ISP and MD probes)
Recruitment duration	6 years
Follow up duration	12 months
Planned Trial Period	1 January 2021 – 31 December 2028
Objectives	Outcome Measures
Primary To determine if the addition of duroplasty to bony decompression improves motor outcome after TSCI	Change in AIS motor score (6 months post-randomisation minus pre-operative baseline)

Secondary To determine if the addition of duroplasty to bony decompression: 1. Improves functional outcomes after TSCI 2. Improves quality of life after TSCI 3. Is safe 4. Improves MRI features 5. Improves physiology, metabolism and inflammation at injury site	1. AIS (light touch, pinprick, grade) at 6 months; CUE-Q, grip strength, WISCI-II, SCIM-III at 6 months 2. SF-36 at 6 and 12 months 3. No. of re-operations on spine at 12 months; Complications, adverse events, mortality and length of hospital stay all at 12 months 4. Cord tether, syrinx, spinal deformity at 6 months 5. ISP, SCPP; Injury site glucose, lactate, pyruvate, glutamate, glycerol, LPR; Injury site cytokines

iv. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Management Committees

Aim: To outline the various committees or groups involved in trial coordination and conduct.

- **Trial Steering Committee**

  The TSC will ensure that:

  - Progress is satisfactory and the study is adhering to its overall objectives as set out in the protocol.
  - Patient safety is not being compromised.
  - The study is being conducted in accordance with Good Clinical Practice (GCP).

Decisions about continuation or termination of the study are usually the responsibility of the TSC. They will provide information and advice to the Sponsor, Funder and TMG in this regard.

Meetings of the TSC will take place annually, or at shorter intervals if deemed necessary.

The TSC will adopt a Charter as per OCTRU SOPs, which details further roles and responsibilities of the committee and will be stored in the electronic Trial Master File (eTMF).

- **Data and Safety Monitoring Committee**

The DSMC will review all SAEs (and AEs if requested) reported for the trial at each DSMC meeting. The DSMC will evaluate the risk of the trial continuing and will take appropriate action where necessary.

The DSMC will safeguard the interests of trial participants, potential participants and future participants, to assess the safety and efficacy of the interventions during the trial, and to monitor the overall conduct of the trial, protecting its validity and credibility. The DSMC will adopt a DAMOCLES based charter which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, see copies of data accrued to date, or summaries of that data by treatment group. They will also consider emerging evidence from other trials or research on the intervention. They may advise the chair of the TSC at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety.

DSMC meetings will be held at least once a year during the recruitment phase of the study and the open reports and a letter from the DSMC Chair will be forwarded to the TSC Chair after each meeting. The TSC will ultimately have the final say in stopping the trial early.

The DSMC will adopt a Charter as per OCTRU SOPs, which details further roles and responsibilities of the committee and will be stored in the electronic Trial Master File (eTMF)

- **Trial Management Group**

The TMG will meet every month throughout the duration of the trial with addition meetings as deemed necessary up to the close of recruitment – then frequencies may be revised. During the trial set up phase these meetings will be more infrequent and determined by the progress of the trial set up.

The TMG will:

- Supervise the conduct and progress of the study, and adherence to the study protocol.
- Assess the safety and efficacy of the interventions during the study.
- Monitor the safety of the participants, and review safety data to look for any emerging trends including increases in severity or frequency of SAEs or SARs (which may require expedited reporting to the relevant REC).
- Evaluate the quality of the study data.

Escalate any issues for concern to the Sponsor, specifically where the issue could compromise patient safety or the integrity of the study or quality of the study data.

The TMG will adopt a Charter as per OCTRU SOPs, which details further roles and responsibilities of the committee and will be stored in the electronic Trial Master File (eTMF).

v. Funder:

This project (NIHR130048) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.

vi. Protocol contributors

The protocol should:

1. Describe the input of relevant expertise from individuals for example, statisticians, pharmacists, pathologists and radiation experts.

See 'Key Protocol Contributors' in 'Key Study Contacts' section on page 3

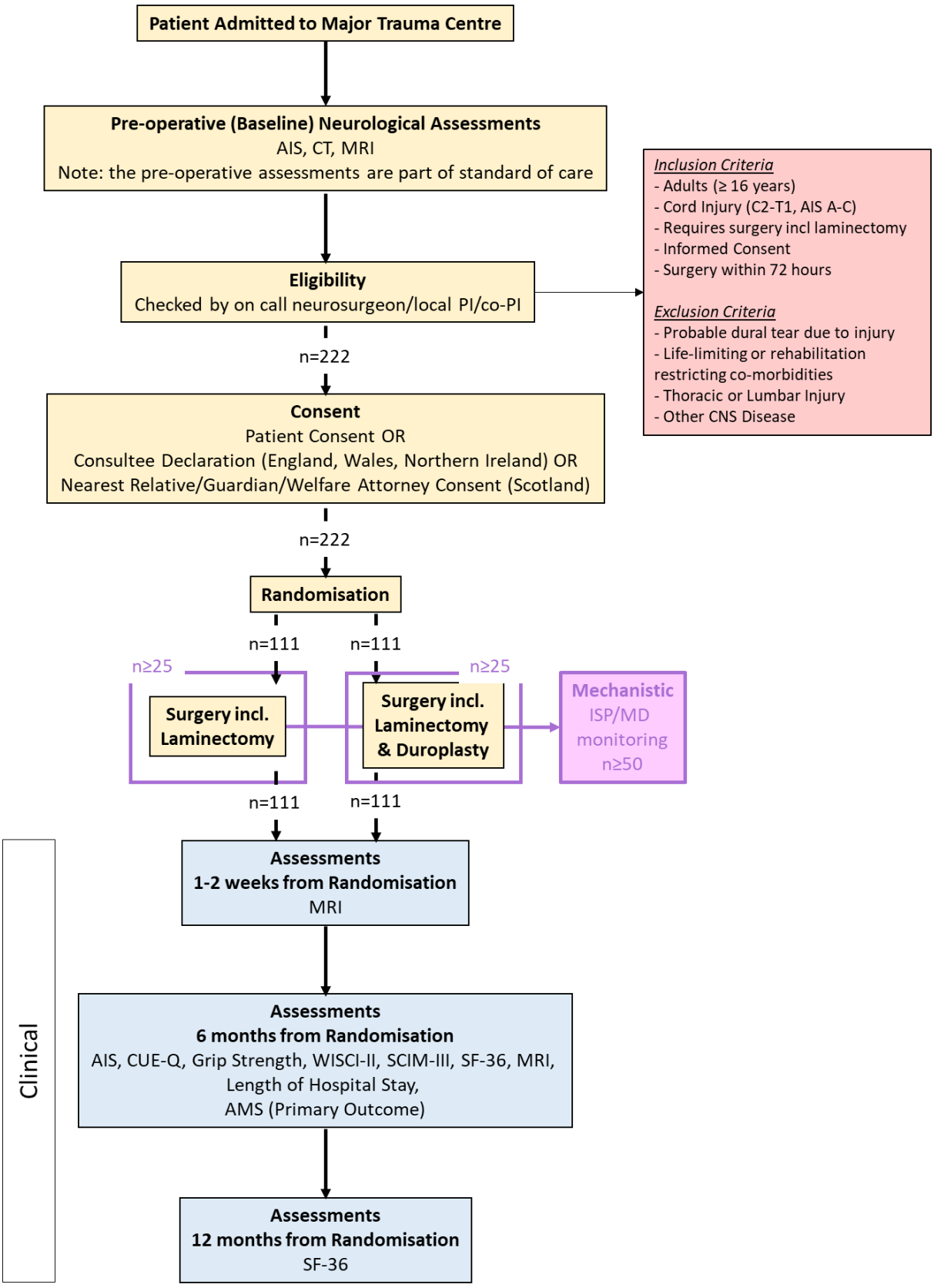
This trial is focused on improving the quality of life of patients with spinal cord injuries. It was designed with help from the Spinal Injuries Association and patients with spinal cord injuries who were actively involved in the trial conception, design and development. Patient meetings were held to discuss the 'patient facing documents and other materials' (PIS/ICF) for both the main trial and mechanistic study, consenting process and outcome measures.

Patients with cord injuries are involved in the running of the trial and comprise both co-applicants and committee members.There is no use of radioactivity or X-Rays as part of the DISCUS study. The CT before the surgery is done before the patient is recruited into the DISCUS trial and is part of standard of care. The MRI scans do not involve radioactivity or XRays.

vii. Participation in NIHR Associate Principal Investigator Scheme

Please note that DISCUS is part of the NIHR associate principal investigator (PI) scheme (https://www.nihr.ac.uk/health-and-care-professionals/career-development/associate-principal-investigator-scheme.htm).

viii. TRIAL FLOW CHART



1 BACKGROUND

We plan to investigate expansion duroplasty as a novel treatment for acute, severe traumatic spinal cord injury (TSCI) in a randomised controlled trial (led by M. Papadopoulos as co-C.I.) and characterise the underlying mechanisms (mechanistic study led by S. Saadoun as co-C.I.). In the UK, TSCI affects about 1,000 people annually, i.e. one person suffers a TSCI every 8 hours; it is estimated that there are 40,000 patients currently living with the condition [McDaid et al., 2019]. The age distribution is bimodal with a peak in young adults (16 – 35 years), primarily caused by sport and road traffic accidents, and a second peak in the elderly (>65 years) primarily caused by falls [van den Berg et al., 2010]. Life expectancy after TSCI is reduced; in the UK, a 20-year-old male first year survivor with severe cervical TSCI has 46 – 67 % the life expectancy of a healthy 20-year-old [Savic et al. 2017]. TSCI mostly affects adults in their economic prime; 78 % are male with a mean age at injury of 43 years [NSCISC, 2016].

TSCI is a devastating condition that causes partial or total limb paralysis, loss of sensation below the injury, difficulty breathing, loss of bladder and bowel control and loss of sexual function. Patients with TSCI are extremely vulnerable to complications; commonly occurring co-morbidities are pressure ulcers, chronic pain, spasticity, joint stiffness, muscle contractures, delayed neurological deterioration from enlarging cord cyst (syrinx), pneumonia, urosepsis and hypotension [Sweis et al., 2017].

The effects of TSCI extend beyond the individual and impact on their families and society; anxiety, depression, unemployment, breakup of relationships and dependence are common in TSCI patients [Lim et al., 2017], whilst their caregivers report high levels of burden [Scholten et al., 2018]. TSCI patients are a significant burden on the NHS and are frequently admitted to hospital with problems that require lifelong treatment [Sweis et al., 2017]. The financial burden is substantial: the mean lifetime treatment cost / patient for severe (AIS A – C) cervical TSCI is US$ 1.4 million in the USA [SCI, 2019] and CAN$ 0.4 million in Canada [Chan et al., 2019], excluding loss of earnings and productivity; equivalent costs are not available for the UK.

To date, no treatments have been shown to improve outcome after TSCI. Improved neurological (motor, sensory, autonomic function) and quality of life outcomes, achieved by duroplasty, will have obvious benefit for patients and relatives, substantial health gains for society and significant economic implications. Proven benefit from duroplasty in a RCT means that this procedure would be immediately applied as standard care across the NHS, in all 26 MTCs. Such surgical intervention would have clear global appeal and worldwide impact. Duroplasty takes only 10 – 15 minutes to perform and is inexpensive; a 1 x 3 inch Durapair® patch (Medtronic) costs about £100. Thus, there are few barriers in terms of it being adopted into clinical practice within the UK and worldwide.

2 RATIONALE

OVERALL AIM: To determine whether expansion duroplasty improves outcome after TSCI.

WHY THIS RESEARCH IS NEEDED NOW: In a systematic review, patients with cervical TSCIs identified improvements in arm and hand function, bladder and bowel function, sexual function and personal relationships with families and friends as priorities that will ultimately improve their quality of life [Simpson et al., 2012]. Here, we hypothesise that the addition of expansion duroplasty to standard treatment will reduce spinal cord compression, improve SCPP, spinal cord metabolism and reduce spinal cord inflammation at the injury site. These physiological and metabolic benefits are predicted to increase neuronal survival thus improving motor outcome that will lead to improved limb function as well as improved bladder and bowel control, ultimately improving patient quality of life. We thus propose investigating the impact of duroplasty on spinal cord physiology, metabolism and inflammation, motor and sensory scores and health related quality of life (HRQoL) measures including

hand function, walking, bladder and bowel function as well as mental and emotional health and social well-being.

In the UK, TSCI patients are initially admitted to Major Trauma Centres (MTCs). Most have surgery that involves fixing the spine with instrumentation (screws, rods) to reduce deformity/instability and bony decompression by laminectomy. Current emphasis is on the detrimental effect of bony compression; thus, most surgeons (85 – 96 %) advocate bony decompression for treatment of TSCI [NICE, 2016]. However, whether bony decompression improves outcome after TSCI is controversial, according to NICE guidelines, due to lack of supporting evidence from RCTs [NICE, 2016]. We propose that bony decompression without duroplasty will only partially decompress the swollen, injured cord, which remains compressed against the dura, which may explain why the benefit of bony decompression after TSCI remains uncertain. Surgical intervention to achieve adequate cord decompression is particularly important in this setting as there are no drug treatments that have been shown to improve outcome in patients with acute, severe TSCI. Though methylprednisolone administration was initially shown to be beneficial, subsequent trials, observational studies and meta-analyses revealed lack of efficacy and possible harm [Liu et al., 2019]. Given the uncertainty of optimum treatment for patients, the management of TSCI, including medical, anaesthetic and surgical management, in the UK varies widely between MTCs including target blood pressure, type of anaesthetic agent, extent of monitoring (use of arterial and central lines) and timing of surgery [Werndle et al., 2012]. DISCUS was designed to avoid these controversies by allowing recruiting centres to time the surgery and medically manage their patients according to local practices. Any influence of variations in the timing of surgery and in the medical management on our outcome measures are expected to balance between the two trial arms of DISCUS given the randomized nature of the study.

PROOF OF CONCEPT: We propose that the dura (non-stretchable membrane around the spinal cord) is a major, but unappreciated, cause of cord compression, i.e. the swollen cord is compressed against the dura, causing high ISP, low SCPP and further cord damage. We hypothesise that bony decompression without dural decompression (current management) does not effectively reduce ISP. DISCUS will investigate a novel surgical treatment (duroplasty) to relieve dural compression. Duroplasty involves sectioning the dura longitudinally and suturing a dural patch to expand the space around the injured cord aiming to reduce ISP and enhance cord perfusion [Phang et al., 2015]. After duroplasty, the injured cord swells into the additional intradural space that has been created. There are several lines of evidence supporting the potential benefit of duroplasty:

1. Exploratory studies: Our exploratory (feasibility, pilot) study assessed safety and the effect on ISP and SCPP of duroplasty after TSCI by comparing bony decompression in 11 patients *versus* bony + dural decompression in 10 [Phang et al., 2015]. Duroplasty was found to be safe: 50 % patients had non-compressive pseudo-meningocele that disappeared at 6 months, with no wound infection, no persistent cerebrospinal fluid (CSF) leak and no worsening neurology. Compared with bony decompression, bony + dural decompression reduced ISP by ~10 mmHg and increased SCPP by ~15 mmHg. There are other reports of TSCI patients treated with bony decompression + duroplasty without complications [Grassner et al., 2017; Zhang et al., 2016; Zhu et al., 2019]. Duroplasty is commonly performed to treat Chiari malformation, with ample evidence indicating its safety [Chotai et al., 2014; De Vlieger et al., 2019; Del Gaudio et al., 2018; Dlouhy et al., 2018; Elhadji Cheikh Ndiaye et al., 2019; Lin et al., 2018].

2. Evidence from ISP monitoring. As part of our ISCoPE study (St. George's Hospital), we insert intradurally at the injury site a pressure probe (monitors ISP and SCPP of swollen cord) [Werndle et al., 2014] and a MD catheter (monitors injury site metabolism) [Phang et al., 2016]. A key finding is that ISP remains high with low SCPP even after anterior + posterior bony decompression [Werndle et a., 2014; Hogg et al., 2019] thus suggesting the dura contributes to cord compression.

3. Evidence from MRIs. In a cohort of TSCI patients (n=65) without bony compression, dural compression was evident on MRI as lack of cerebrospinal fluid (CSF) around the injured cord [Saadoun et al., 2016]. The extent of dural cord compression increased with increasing severity of TSCI and resolved slowly ($t_{1/2}$ = 9 days).

4. Animal studies. Reducing ISP by duroplasty or genetic manipulation to limit cord swelling improved outcome in numerous rodent TSCI models [Zhang et al., 2016; Fernandez et al., 1985; Iannotti et al., 2006; Jalan et al., 2017; Saadoun et al., 2008; Smith et al., 2010]. These studies show that, after TSCI, the cord swells against the dura from a combination of cord haematoma and oedema. In rat models, duroplasty has beneficial effects other than lowering ISP, including less cord inflammation, less cord scarring and smaller syrinx. The studies suggest that fibrin sealants may cause cord compression and we have, therefore, avoided their use in our duroplasty trial.

5. Analogy with brain injury. The dura is unstretchable (high Young modulus) [Wilcox et al., 2003]. It is established that the dura compresses swollen brain; thus, decompression for brain injury is bony + dural decompression, shown to lower mortality in an NIHR-funded RCT (RESCUEicp) in which two DISCUS investigators played key roles: M. Papadopoulos (Local Investigator, St. George's), P. Hutchinson (Chief Investigator) [Hutchinson et all., 2013].

CONSENSUS AMONGST PATIENTS AND CLINICIANS: Prior to developing the proposal for this study a number of meetings with clinicians (both nationally and internationally) and patients took place: Dr. Saadoun organized a consensus meeting in London in November 2018, sponsored by Wings for Life, where 41 specialists in neurosurgery, neurointensive care (NICU), neurology, neurorehabilitation, neuroscience and patient advocates came together to discuss and agree on the proposed DISCUS trial [Saadoun, 2018]. The DISCUS trial was also discussed with the Spinal Injuries Association (SIA) at St. George's in May 2019 focussing on the consenting process, patient information and outcome measures. In addition, the DISCUS trial was discussed in a Special Session at the ICP2019 meeting in October 2019 in Leuven. The consensus was that there is overwhelming support from both patients and the clinical community for this trial with agreement that there was scope to improve outcome for patients with TSCI. Patient feedback included increasing the time window from consent to participation, dissemination of findings through the Spinal Injuries Association (SIA) and to include functional bladder and bowel outcomes, all of which have been included in the current study design.

A RCT would be the next step to provide evidence that duroplasty improves motor function in patients with TSCI and to change clinical practice within the UK and worldwide. Centres worldwide are currently performing duroplasty in TSCI patients without robust randomised evidence; the proposed study would be the first RCT to address this question. Additionally, there is great scope for a surgical trial to improve outcome for patients; there are currently no other RCTs available to patients with TSCI within the UK.

OVERALL DESIGN: DISCUS is a phase III clinical trial designed to determine the clinical effectiveness of expansion duroplasty, compared with current treatment. DISCUS aims to assess improvement in limb motor scores at 6 months compared with baseline with secondary outcomes assessing function, quality of life, MRI appearances and safety.

P – Patients ≥16 years old with acute, severe TSCI.
I – Patients will have surgery within 72 hours of TSCI including laminectomy spanning the length of swollen cord on the pre-operative MRI as well as dorsal duroplasty by suturing an elliptical patch of artificial dura about 1 cm longer than the dural incision and about 2 cm wide to the dural edge.
C – Standard of care surgery within 72 hours of injury to include laminectomy spanning the length of swollen cord on the pre-operative MRI without duroplasty.

O – Improvement in AIS motor score at 6 months compared with AIS motor score (AMS) at baseline (ΔAMS).

MECHANISTIC STUDY: DISCUS includes an optional study (led by Dr. Saadoun) to determine the underlying mechanisms by which duroplasty improves outcome, i.e. whether expansion duroplasty reduces cord compression, improves cord perfusion, reduces cord ischaemia and reduces cord inflammation. Any patient recruited into DISCUS is eligible for the mechanistic study; whether the patient participates in the monitoring study at a particular centre depends on whether the local neurosurgery unit / ICU elect to carry out ISP monitoring or MD monitoring or both. All neurosurgery units have equipment to monitor pressure, which is routinely used for severe brain injuries, and therefore ISP monitoring should be straightforward. Only some neurosurgery units have equipment to monitor MD. DISCUS will not purchase equipment for the mechanistic study but will contribute funds to cover costs of pressure probes and MD catheters and solutions.

P – Patients ≥16 years old with acute, severe TSCI.
I – Patients will have surgery within 72 hours of TSCI including laminectomy spanning the length of swollen cord on the pre-operative MRI as well as dorsal duroplasty by suturing an elliptical patch of artificial dura about 1 cm longer than the dural incision and about 2 cm wide to the dural edge. A pressure probe and/or a MD catheter will be inserted intradurally at the injury site.
C – Standard of care surgery within 72 hours of injury to include laminectomy spanning the length of swollen cord on the pre-operative MRI without duroplasty. A pressure probe and/or a MD catheter will be inderted intradurally at the injury site.
O – Mean daily values of ISP, SCPP, injury site metabolites, injury site cytokines

2.1 Assessment and management of risk

RISKS OF EXPANSION DUROPLASTY: Expansion duroplasty has been reported in two case series of patients with acute, severe TSCI [Phang et al., 2015; Rooshenas et al., 2019], despite it being performed in centres worldwide. This procedure is widely performed in patients with Chiari malformation to decompress the cranio-cervical junction [Chotai et al., 2014; De Vlieger et al., 2019; Del Gaudio et al., 2018; Dlouhy et al., 2018; Elhadji Cheikh Ndiaye et al., 2019; Lin et al., 2018]. Experience from adult TSCI and Chiari patients from 2010-9 (Table below) shows that the commonest complications are CSF-related, i.e. CSF leak through the wound, which resolves with lumbar CSF drainage for 5 – 10 days, and pseudomeningocele, which resolves spontaneously in TSCI but requires re-operation in 1 % of Chiari patients. The incidence of wound infection is low (<1 %) and easily treated with antibiotics. The serious complication of septic meningitis is rare, i.e. not observed in these series. 9 % of Chiari patients develop aseptic meningitis, a benign condition not reported in duroplasty for TSCI. Because DISCUS only includes patients with cervical TSCI, CSF leak and pseudomeningocele could be reduced by sitting the patient at 45^{o} for a week to limit cervical CSF pressure. The Table below shows the complications of expansion duroplasty for TSCI and for Chiari I malformation. Together, these findings indicate that duroplasty in the cervical region is safe.

COMPLICATION	PATIENTS NO.	%	COMMENT
Duroplasty for TSCI [Phang et al., 2015; Zhu et al., 2019]			
CSF leak	4 / 26	10	Treated successfully with lumbar drain
Wound infection	0 / 26	0	
Meningitis (septic)	0 / 26	0	
Pseudomeningocele	5 / 26	19	All resolved at 6 month MRI
Chiari I malformation [Chotai et al., 2014; De Vlieger et al., 2019; Del Gaudio et al., 2018; Dlouhy et al., 2018; Elhadji Cheikh Ndiaye et al., 2019; Lin et al., 2018]			
CSF leak	9 / 277	3	Treated with lumbar drain
Wound infection	4 / 277	1	Successfully treated with antibiotics
Meningitis (NB. aseptic)	24 / 277	9	Self-limiting, responds to steroids
Meningitis (septic)	0 / 277	0	
Pseudomeningocele	10 / 277	4	3 patients required re-operation

REDUCING RISKS OF DUROPLASTY: Several technical nuances may minimise the risks of infection, CSF leak and pseudomeningocele:

1. Use of nylon sutures for skin closure, which are more watertight than staples.
2. Applying a waterproof film dressing (e.g. Ioban®, which is a betadine impregnated adhesive dressing) over the wound for one week.
3. Postoperative intravenous antibiotic prophylaxis dictated by local policy.
4. Placing the wound drain *in situ* on gravity (rather than suction) for one week.
5. We discourage use of Tisseel glue, which is widely used in neurosurgery to reduce CSF leak, because this product expands and may thus itself cause spinal cord compression.
6. Sitting up the patient to $>45^0$ for a week to reduce cervical CSF pressure.
7. Removing the sutures at two weeks.
8. Suturing the dural patch to dura, rather than merely applying the duroplasty without suturing it.
9. Sutures to tighten the skin around the probes to reduce CSF leak (mechanistic studies).

The above measures will be discussed with the surgeons at each participating site and will be part of the online training course for participating centres but will not be imposed. Patient management will be left to the local clinical teams. These data will be documented in the CRF.

RISKS OF ISP AND MD MONITORING: In 2018, we published the safety profile of injury site monitoring for up to a week in a cohort of 42 AIS A – C TSCI patients (including cervical and thoracic injuries) treated at St. George's Hospital in London (Table below). The most common complications are CSF related and easy to manage by adding extra sutures to the wound or spontaneously resolve. These findings suggest that injury site monitoring in TSCI patients is a safe technique.

COMPLICATION	PATIENTS NO.	%	COMMENTS
CSF leak	3 / 42	7	Resolved by wound re-suturing
Wound infection or breakdown	0 / 42	0	
Meningitis (septic)	0 / 42	0	
Pseudomeningocele	8 / 42	19	All resolved at 6 month MRI
Probe displacement	1 / 42	2	
Neurological deterioration	0 / 42	0	
Haematoma	0 / 42	0	

TRIAL SAFETY: DISCUS will run in accordance with OCTRU's Standard Operating Procedures (SOPs) and operational policies, which adhere to all applicable UK regulatory requirements. The trial will be overseen by a DSMC and a TSC. The project will also be monitored by the sponsor (City St George's, University of London).

The DISCUS trial is categorised as:

- ~~Type A = No higher than the risk of standard medical care~~
- **Type B** = Somewhat higher than the risk of standard medical care
- ~~Type C = Markedly higher than the risk of standard medical care~~

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

PRIMARY OBJECTIVE: To determine if, in patients with severe cervical TSCI, bony + dural decompression improves AMS at 6 months compared with bony decompression alone.

POPULATION: We aim to recruit 222 adults with acute, severe cervical TSCI to achieve 85% study power. We may increase recruitment to 260 patients to achieve 90% power, dependent on recruitment from international sites.
Note: We exclude thoracic TSCIs because most have severe injuries with complete paralysis without any significant spontaneous motor recovery because the AIS motor scores are not sensitive to segmental recovery in the thoracic region.

INTERVENTION: Surgery (approach, instrumentation) is at the surgeon's discretion, but will include laminectomy spanning the length of swollen cord on the pre-operative MRI. Patients will have dorsal duroplasty by suturing an elliptical patch of artificial dura approximately 1 cm longer than the dural incision and approximately 2 cm wide to the dural edge. We recommend that a wound drain be placed on gravity and the skin sutured and covered with waterproof adhesive film dressing such as Ioban,
Note: Ioban is an iodine impregnated dressing that minimises the risk of wound infection and of CSF leak.
The wound drain and dressing is typically removed at 1 week and the sutures at 2 weeks. CSF leak is normally treated by placing extra sutures or a lumbar drain.

CONTROL: Standard of care surgery to include laminectomy.

OUTCOME: Improvement in AIS motor score at 6 months compared with AMS at baseline (ΔAMS).

TIMECOURSE: This project will last for a total of 96 months. Patients will be followed for 12 months after randomisation.

There will be formal stop/go review in month 15, (i.e. after 9 months of recruitment) to ensure a minimum of 5 patients have been randomised from a minimum of two centres. If the target is met, the trial will continue to completion. This 15-month formal stop/go criterion is a contractual agreement with the NIHR. One TSC meeting will be held at month 12-14 (i.e. before the formal stop/go review) and yearly thereafter unless an emergency meeting is required. The TSC will also receive information from the QRI that may require further meetings depending on recruitment.

3.2 Secondary objectives

1 (Neurology): To determine if, in patients with severe cervical TSCI, bony + dural decompression improves neurological outcome as defined by the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI).

2 (Function): To determine if, in patients with severe cervical TSCI, bony + dural decompression improves functional outcomes at 6 months compared with bony decompression alone.

3 (Quality of life): To determine if, in patients with severe cervical TSCI, bony + dural decompression improves HRQoL at 6 and 12 months compared with bony decompression alone.

4 (Mechanism): To determine if, in patients with severe cervical TSCI, bony + dural decompression improves MRI features, improves spinal cord perfusion and reduces spinal cord inflammation at the injury site, compared with bony decompression alone.

5 (Safety): To determine if, in patients with severe cervical TSCI, bony + dural decompression is safe.

3.3 Outcome measures/endpoints

PRIMARY OUTCOME: Change in AIS motor score at 6 months versus baseline (ΔAMS).

The primary outcome is a standardised tool. The 2019 AIS ISNCSCI is a validated clinician-administered scale which is used to classify severity of injury in individuals with TSCI, taking around 30 – 60 minutes to complete. It is widely used in clinical and research settings to fully assess sensory and motor functioning and level of injury in TSCI patients. It has high inter- and intra-rater (ICC > 0.99) reliabilities and strong correlations (r > 0.9) with functional scores including Quadriplegia Index of Function (QIF) and Functional Independence Measure (FIM). ISNCSCI is the preferred instrument in clinical practice to assess the neurological deficit caused by the TSCI [SCIRE Professional, 2016]. For intubated TSCI patients, sedation will be lightened sufficiently to allow assessment, and this will be at the discretion of the local doctors.

The proposed primary outcome, the AIS Motor Score (AMS), is part of the ISNCSCI (also known as ASIA assessment) and is conducted by testing and scoring five myotomes in each limb, each rated 0 – 5, giving a total score between 0 – 100. Changes in motor scores or equivalent have been used widely in SCI trials including RISCIS (NCT01597518, ΔAMS 0 – 6 months), NISCI (NCT03935321, upper limb ΔAMS 0 – 6 months), MASC (NCT01828203, ΔAMS 0 – 3/6/12 months), MAPS (NCT02232165, ΔAMS 0 – 12 months) and CSFD (NCT02495545, ΔAMS 0 – 6 months).

ISNCSCI requires physical examination of the patient by a competent examiner (such as a physiotherapist) rather than a simple telephone assessment. We will require examiners to provide evidence that they have been trained, e.g. by completing the International Standards Training course (https://lms4.learnshare.com/dashboard/dash.home.aspx?Z=0itApFGWTBr1Dh0rqKXQPSEwXn9LfMnBl73Qk7jP5PM%3d&LSMID= The consensus from the patient focus groups is improvement in motor function as assessed by the AMS is a more meaningful outcome to patients in this setting than assessment by a HRQoL questionnaire. Participants in the trial will have the ISNCSCI examination performed on admission before surgery by neurosurgeons at the MTC (prior to randomisation) and at 6 months as part of their routine assessments at the spinal injuries unit by a physiotherapist or rehabilitation doctor. Therefore, the primary outcome measure is within the current standard of care and widely acceptable in the field to both patients and clinicians.

SECONDARY OUTCOMES (NEUROLOGY):

1. Change in AIS sensory score (light touch) at 6 months compared with baseline.
2. Change in AIS sensory score (pin prick) at 6 months compared with baseline.
3. Change in AIS grade at 6 months compared with baseline.

1. – 3. are standardised tools. We will quantify sensation (light touch, pinprick) using standard scales at 6 months versus baseline. The sensory outcomes are part of the ISNCSCI assessment and are conducted by testing and scoring 28 dermatomes on the left and 28 on the right as 0 (no sensation), 1 (reduced sensation) or 2 (normal sensation) giving a total score 0 – 112 for light touch and 0 – 112 for pinprick. From the ISNCSCI assessment, we will derive the AIS grade (A, B, C, D, E) as defined in the Table.

GRADE	DEFINITION	EXPLANATION
A	Complete	No sensory or motor function is preserved in the sacral segments S4-5.
B	Sensory Incomplete	Sensory but not motor function is preserved below the injury level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.
C	Motor Incomplete	Motor function is preserved at the most caudal sacral segments for voluntary anal contraction OR the patient meets the criteria for sensory incomplete status by light touch, pin prick or deep anal pressure, and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. <50 % of key muscle functions below the level of injury have muscle grade ≥ 3.
D	Motor Incomplete	Motor incomplete as defined above, with ≥50 % of key muscle functions below the neurological level of injury having muscle grade ≥ 3.
E	Normal	Sensation and motor function graded as normal in all segments.

SECONDARY OUTCOMES (FUNCTION):

4. CUE-Q (to assess upper limb function) at 6 months.
5. Hand grip strength using a dynamometer at 6 months.
6. WISCI-II (to assess walking ability) at 6 months.
7. SCIM-III (to assess self-care and daily living) at 6 months.

SECONDARY OUTCOMES (QUALITY OF LIFE):

8. SF-36 at 6, 12 months.

4. – 8. are standardised tools. We will use these functional scales, which are established in TSCI, to confirm that the motor improvement that we seek is associated with functional improvements: CUE-Q (hand function), grip strength, WISCI II (walking) and SCIM III (independence measure that includes sphincter function and validated in TSCI). In addition, we use one a HRQoL scale as a secondary outcome measure (SF-36,) aiming to show that the functional improvement translates to improvement in HRQoL.

SECONDARY OUTCOMES (SAFETY)

9. Number of re-operations required on the spine within 12 months
10. Total length of hospital stay (Stay in MTC, stay in spinal injury unit, other hospital admissions)
11. Surgical complications and adverse events – recorded postoperatively and at follow-up visits
12. Overall survival (OS) – time from randomisation to death or end of follow-up (1 year)
13. MRI 2 weeks: Size of pseudomeningocele
14. MRI 6 months: Spinal deformity (Cobb angle between superior C2 and inferior C7 endplates); Size of pseudomeningocele,

9. – 12. are objective measures that yield the same value independent of assessor. 14. (spinal deformity) Is a standardised tool. Safety of duroplasty will be assessed in different ways, not only by comparing complications and adverse events, but also by determining the number of re-operations on spine, total hospital stay, OS as well as spinal deformity in the duroplasty versus the non-duroplasty arms.

SECONDARY OUTCOMES (MECHANISM):

15. MRI at 2 weeks (all patients):
    a. Length of cord compression (no CSF around the cord in mid-sagittal MRI)
16. MRI at 6 months (all patients):
    a. Length of cord tether
    b. Length of cord syrinx
17. Pressure monitoring at injury site (mechanistic study patients):
    a. Mean daily ISP
    b. Mean daily SCPP
18. MD monitoring at injury site (mechanistic study patients):
    a. Mean daily metabolites (glucose, lactate, pyruvate, LPR, glutamate, glycerol)
    b. Mean daily cytokines (GROα, IL1α, IL1β, IL4, IL8, IL10, IP10, MCP1, MIP1α, MIP1β) or others.

15. and 16. are not standard measures because they are particular for DISCUS and will be measured on MRI by two radiologists. 17. and 18. are objective measures independent of assessor. The aim is to determine the mechanism by which duroplasty improves outcome. We will investigate if dural + bony decompression more effectively decompresses the swollen cord than bony decompression alone, i.e. lower ISP, higher SCPP, CSF around injured cord (MRI). More effective decompression by duroplasty is predicted to improve spinal cord metabolism, compared with bony decompression alone, i.e. more energy (higher glucose), less ischaemia (lower lactate, higher pyruvate and lower LPR), less excitotoxicity (lower glutamate) and less cell death (lower glycerol). More effective decompression by duroplasty is also predicted to reduce cord inflammation, compared with bony decompression alone, i.e. lower GROα, IL1α, IL1β, IL4, IL8, IL10, IP10, MCP1, MIP1α, MIP1β. In the long-term (6 months), the extra space created by duroplasty is predicted to reduce cord tethering at the injury site and spinal cord syrinx.

3.4 Primary endpoint/outcome

Change in AIS motor score at 6 months versus baseline (ΔAMS).

3.5 Secondary endpoints/outcomes

- Change in AIS sensory score (light touch) at 6 months compared with baseline (all patients)
- Change in AIS sensory score (pin prick) at 6 months compared with baseline (all patients)
- Change in AIS grade at 6 months compared with baseline (all patients)
- CUE-Q (upper limb function) at 6 months (all patients)
- Grip strength (hand function) at 6 months (all patients)
- WISCI-II (walking ability) at 6 months (all patients)
- SCIM-III (self-care and daily living) at 6 months (all patients)
- SF-36 at 6 and 12 months (all patients)
- Number of re-operations required on the spine within 12 months (all patients)
- Total length of hospital stay (Stay in MTC, stay in spinal injury unit, other hospital admissions) (all patients)
- Surgical complications and adverse events – recorded postoperatively and at follow-up visits

- OS – time from randomisation to death or end of follow-up (1 year) (all patients)
- MRI at 6 months: Spinal deformity (Cobb angle between the superior endplate of C2 to the inferior endplate of C7) (all patients)
- MRI at 2 weeks: Length of cord compression (no CSF around the cord in mid-sagittal MRI), Size of pseudomeningocele
- MRI at 6 months: Length of cord tether, Length of cord syrinx (all patients), Size of pseudomeningocele
- Pressure monitoring at injury site: Mean daily ISP, Mean daily SCPP (mechanistic study patients)
- MD monitoring at injury site: Mean daily metabolites (glucose, lactate, pyruvate, LPR, glutamate, glycerol), Mean daily cytokines/chemokines (GROα, IL1α, IL1β, IL4, IL8, IL10, IP10, MCP1, MIP1α, MIP1β, or others) (mechanistic study patients)

Objective	Outcome Measure	Timepoint(s) of evaluation of this outcome measure
PRIMARY: To determine if bony + dural decompression improves motor score	Change in AIS motor score	6 months minus baseline
SECONDARY 1: To determine if bony + dural decompression improves neurological outcome	Change in AIS sensory score (light touch)	6 months minus baseline
	Change in AIS sensory score (pin prick)	6 months minus baseline
	Change in AIS grade	6 months minus baseline
SECONDARY 2: To determine if bony + dural decompression improves functional outcomes	CUE-Q	6 months
	Grip strength	6 months
	WISCI-II	6 months
	SCIM-III	6 months
SECONDARY 3: To determine if bony + dural decompression improves quality of life	SF-36	6, 12 months
SECONDARY 4: To determine if bony + dural decompression improves MRI features, improves cord perfusion and reduces cord inflammation at the injury site.	MRI length of cord compression (no CSF around the cord in mid-sagittal MRI)	2 weeks
	MRI size of pseudomeningocele (cranio-caudal, antero-posterior, medio-lateral lengths, and estimated volume)	2 weeks, 6 months
	MRI Length of cord tether in mid-sagittal MRI	6 months
	MRI Mid sagittal length of cord syrinx	6 months
	Pressure monitoring at injury site: mean daily ISP (mechanistic study patients only)	Up to 5 days after surgery
	Pressure monitoring at injury site: mean daily SCPP (mechanistic study patients only)	Up to 5 days after surgery
	MD monitoring at injury site: mean daily glucose, lactate, pyruvate, LPR, glutamate, glycerol (mechanistic study patients only)	Up to 5 days after surgery

	MD monitoring at injury site: mean daily cytokines (GROα, IL1α, IL1β, IL4, IL8, IL10, IP10, MCP1, MIP1α, MIP1β) (mechanistic study patients only)	Up to 5 days after surgery
SECONDARY 5: To determine if bony + dural decompression is safe.	Number of re-operations on spine	12 months
	Total hospital stay	12 months
	Complications and adverse events	12 months
	Overall survival (OS): from randomisation to death or end of follow-up	12 months
	MRI Spinal deformity: Cobb angle between superior C2 and inferior C7 endplates	6 months

4 TRIAL DESIGN

DISCUS is a randomised, controlled multi-centre trial with two trial arms: 1) surgical decompression including laminectomy (standard of care, control), and 2) surgical decompression including laminectomy + duroplasty. It is a superiority trial, i.e. it aims to show that the trial arm that includes duroplasty improves outcome compared to the control arm. It has a parallel group design i.e. participants will be randomised 1:1 to receive only one of the two trial treatments, i.e. standard of care with laminectomy OR standard of care with laminectomy + duroplasty. The trial will be double-blind i.e. neither the patient nor the assessor of the primary outcome measure at 6 months will know the trial treatment. The assessor at 6 months will be a different hospital from the MTC where the surgery took place and they will not have easy access to the MTC clinical records or operation note.

MECHANISTIC STUDY: A subset of patients, at least N = 50 (at least 25 in each arm), will undergo monitoring from the injury site of ISP + SCPP and/or MD, for up to 5 days after surgery. All centres must ensure that patients who consent and are included in the mechanistic sub-study must first consent to participation in the main trial.

INTEGRATED QUINTET RECRUITMENT INTERVENTION (QRI): this is designed to optimise recruitment and informed consent and is embedded during the first two years of recruitment (months 7 – 30).

5 TRIAL SETTING

TYPES OF PARTICIPATING CENTRES:

Two types:

1. Recruiting centres. MTCs, where surgery and post-operative care take place.
2. Rehabilitation centres (Spinal Injuries Units). where the participants are transferred for rehabilitation, once the acute care at the MTCs has finished.

UK RECRUITING CENTRES: We aim to recruit patients from all neurosurgery units at the UK MTCs which treat acute spinal cord injuries:

- Addenbrooke's Hospital Cambridge;
- James Cook University Hospital Middlesborough;
- John Radcliffe Hospital Oxford;

- St Mary's Hospital London;
- St George's Hospital London;
- Royal London Hospital;
- King's College Hospital London;
- Leeds General Infirmary;
- Queen's Medical Centre Nottingham;
- Royal Victoria Infirmary Newcastle;
- Southampton General Hospital;
- Southmead Hospital Bristol;
- Derriford Hospital Plymouth;
- Hull Royal Infirmary;
- Northern General Hospital Sheffield;
- Queen Elizabeth Hospital Birmingham;
- Royal Preston Hospital Lancashire;
- Royal Sussex County Hospital Brighton;
- University Hospital Coventry;
- Salford Royal Hospital and Manchester Royal Infirmary;
- Aberdeen Royal Infirmary;
- Queen Elizabeth Hospital Glasgow;
- Queen's Hospital, Essex;
- Nuffield Orthopaedic Centre, Oxford;
- Royal Stoke University Hospital;
- Walton Centre, Liverpool;
- University Hospital of Wales, Cardiff;
- Royal Victoria Hospital, Belfast
- The Royal Hospital for Children and Young People and Department of Clinical Neurosciences, Edinburgh;

UK REHABILITATION CENTRES: For the 6 month assessments, patients are expected to be at the Spinal Injuries Units (rehabilitation centres) linked to the MTCs where the patients were initially treated. The UK has 11 TSCI rehabilitation centres:

- The Queen Elizabeth National Spinal Injuries Centre, Southern General Hospital, Glasgow;
- The Golden Jubilee North East Regional Spinal Injuries Centre, James Cook University Hospital, Middlesbrough;
- The London Spinal Cord Injury Centre, Royal National Orthopaedic Hospital, Stanmore, London;
- The Yorkshire Regional Spinal Injuries Centre, Pinderfields Hospital, Wakefield;
- Princess Royal Spinal Injuries Centre, Northern General Hospital, Sheffield;
- North West Regional Spinal Injuries Centre, Southport & Formby Hospital, Southport;
- Midlands Centre for Spinal Injuries, Robert Jones & Agnes Hunt Hospital, Oswestry;
- Duke of Cornwall Spinal Treatment Centre, Salisbury District Hospital, Salisbury;
- National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury;
- Welsh Spinal Cord Injury Rehabilitation Centre, Cardiff;
- Spinal Cord Injury Unit for Northern Ireland, Belfast

INTERNATIONAL CENTRES: DISCUS started as a UK study, but expanded to include international centres.It is anticipated that international centres will contribute to the recruitment for DISCUS <50 % of the total number of patients and will be required to seek their own funding to support recruitment.International centres will adopt the DISCUS protocols of patient assessment, follow-up,

investigations, outcomes etc. and randomise via the same process as the UK centres. These international centres will be sponsored by Gemeinnützige Salzburger Landeskliniken Betriebsgesellschaft mbH (SALK), Müllner Hauptstraße 48, 5020 Salzburg, Austria. Changed regulations due to Brexit will be integrated into DISCUS as they become available including UK and EU data sharing, processing and access agreements.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

1. Age ≥16 years
2. Severe cervical (C2 – T1) TSCI (AIS grade A–C)
3. Deemed to require and be suitable for surgery that includes laminectomy by local surgeon
4. Surgery within 72 hours of TSCI
5. Able to provide informed consent (except in emergency) or consultee declaration or proxy consent.

6.2 Exclusion criteria

1. Probable dural tear due to TSCI
2. Life-limiting or rehabilitation-restricting co-morbidities
3. Thoracic or lumbar TSCI
4. Other CNS disease

7 TRIAL PROCEDURES

7.1 Recruitment

7.1.1 Participant identification

All patients admitted to the Emergency department, Neurosurgical ward or Neurosurgical Intensive Care Unit or ICU with a TSCI will be screened for eligibility to include into the DISCUS trial based on clinical presentation. A member of the direct clinical care team will assess potential eligibility of patients based on the inclusion/exclusion criteria in Section 6.1 and 6.2.

7.1.2 Screening

SCREENING ASSESSMENT: Patients are admitted as emergencies to the Emergency Department initially, then Neurosurgical Unit or ICU where initial investigations, management and assessments are made. A baseline ISNCSCI AIS assessment should be standard of care and will be performed on admission and used to assess the severity of injury as AIS grade (grades A – C eligible). Trial specific assessments will only be conducted after participants have given written informed consent (except in emergency) or PLR consent given. Medical history which would preclude eligibility will be obtained from the clinical team, the patient case notes or after discussion with the patient (or patient's representative – if available).

PARTICIPANT RANDOMISATION: Patients who agree to take part will be enrolled to DISCUS +/- the mechanistic study based on their clinical presentation. A unique randomisation number will be allocated to each patient.

After randomisation, a letter will be sent to the patient's GP regarding the DISCUS trial, informing the GP about the patient's participation but not allocation. The rehabilitation centre (Spinal Injuries Unit) that receives the patient after discharge from the MTC will also be informed about the patient's participation into the DISCUS trial. A pseudonymised record of all patients screened, identified as

eligible, approached and invited to take part in the trial will be kept using the SEAR framework [Wilson et al., 2018]. This will be entered electronically onto a screening log). This information will be used to identify any barriers to recruitment and allow improvement measures to be identified and implemented in a timely manner (See section on integrated qualitative research below)

7.2 Consent

RESPONSIBILITY FOR CONSENT: The local Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that any health professional delegated responsibility to screen, discuss the study with patients (or patient legal representatives) and obtain informed consent is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. Health professionals involved in screening and discussing the study will typically be from neurosurgery or ICU and medically qualified, including consultants, specialist trainees, research or clinical fellows. The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence. Each PI also takes responsibility for ensuring that all local GCP certificates are up to date.

TIMING OF CONSENT: Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial. Consent must be taken prior to study randomisation. As much time as possible (at least 2 hours) will be allowed between explaining the study, that includes providing the PIS, and obtaining the consent. This timeframe may be required to enable the person giving consent to digest the information provided before reaching a decision whether to agree to participate.

WITHDRAWAL OF CONSENT: The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. All participants will continue to be followed up as per routine NHS standard of care. Withdrawn participants will be asked whether the data acquired up to the point of withdrawal can be retained. The reason for withdrawal will be recorded in the participant's medical records and in the Care Report Form (CRF). Any intention to utilise such data should be outlined in the consent literature. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner. If a patient decides to withdraw from the DISCUS trial, their GP will be notified, and any data or samples collected will be retained unless the patient wishes for them to be destroyed.

CONSENT OBTAINED FROM PATIENT: Where potential patients fulfil the eligibility criteria, they will be approached by a member of the research or clinical team who will provide the patient information sheet, and where facilities and time allow the patient information video and answer any questions the patient may have. Wherever possible informed consent will be obtained from the patient. If the patient verbally consents to participate but is unable to sign because of hand weakness as a result of the TSCI, then the form will be signed by an independent healthcare professional (IHP) defined as a witness that the patient has consented. This witness is not the person taking consent. This will be documented in the patient's notes.

NON-ENGLISH SPEAKERS: We confirm that DISCUS aims to recruit non-English speakers as per the Equality, Diversity and Human Rights Act. This will be achieved using an interpreter, who is either a member of staff, or the professional telephone or face-to-face Interpreter and Translation service (Language Line) available to each NHS centre.

CONSENT OR CONSULTATION WITH PERSON OTHER THAN THE PATIENT: DISCUS involves patients who have suffered serious cervical TSCI. Some patients may have difficulty breathing thus requiring sedation and ventilation. Most patients will have capacity to provide informed consent, but some patients may have impairment in their level of consciousness from the sedative drugs. In this emergency situation, these sedated patients may not be able to understand the information relevant to the decision, retain the information, use or weigh the information or communicate his or her decision (by any means). In addition, the surgery has to be performed within 72 hours after injury.

ENGLAND AND WALES: DISCUS is classified as intrusive research. The recruitment of sedated patients complies with the Mental Capacity Act 2005:

- The research is connected with an impairing condition affecting the participant (TSCI) and tests a novel treatment (expansion duroplasty).
- Research of equal effectiveness could not be carried out if confined to TSCI participants with capacity because we will not be able to recruit enough patients to obtain meaningful results.
- The RCT has the potential to benefit the participant without imposing a disproportionate burden. The mechanistic study will provide knowledge of the causes of, or treatment or care of others with the same condition, involves negligible risk to the participant and does not interfere significantly with their freedom of action or privacy, and is not unduly invasive or restrictive, based on our experience to date with more than 80 TSCI patients from the ISCoPE study.
- We have arrangements in place to comply with section 32 (consulting carers) and section 33 (additional safeguards including the freedom to withdraw and respect for advanced statements), see Table below.

NORTHERN IRELAND: The Mental Capacity Act (Northern Ireland) 2016 is closely aligned with Mental Capacity Act 2005, which applies in England and Wales.

SCOTLAND: DISCUS complies with Section 51 of the Adults with Incapacity (Scotland) Act 2000:

- Research of a similar nature cannot be carried out on an adult who is capable in relation to such a decision because we will not be able to recruit enough conscious patients to obtain meaningful results.
- The purpose of the research is to obtain knowledge of the treatment or care of the adult's TSCI
- The RCT and the mechanistic study will contribute through significant improvement in the scientific understanding of the adult's incapacity (TSCI) to the attainment of real and direct benefit to the adult or to other persons having the same incapacity.
- The adult does not indicate unwillingness to participate in the research.
- DISCUS (the RCT and mechanistic study) entails only a minimal foreseeable risk to the adult
- The research imposes no discomfort, or only minimal discomfort, on the adult.
- Consent will be obtained from any guardian or welfare attorney who has power to consent to the adult's participation in research or, where there is no such guardian or welfare attorney, from the adult's nearest relative, see Table below.

ENGLAND, WALES	SCOTLAND
1. Personal Consultee a) A person engaged in caring for the participant (not professionally or for payment) or is interested in his/her welfare, and b) Is prepared to be consulted.	*1. Nearest Relative/Guardian or Welfare Attorney* 1A. A guardian or welfare attorney who has power to consent to the adult's participation in research. 1B. If there is no such person, the adult's nearest relative as defined in 87(1) of the Adults with Incapacity Act 2000.
2. Nominated Consultee If no appropriate person can be identified who is willing to act as a personal consultee, we will consult a "nominated consultee", i.e. a person independent of DISCUS appointed in accordance with the Department of Health's guidance.	*2. Welfare Attorney* A person not connected with the conduct of the trial who is: a) the doctor primarily responsible for the adult's medical treatment, or b) a person nominated by the relevant health care provider. A professional legal representative will be approached if it is not reasonably practicable to contact 1A or 1B before the decision to enter the adult into DISCUS is made. Informed consent must be given before the subject is entered into DISCUS.

1. Where patients are unable to provide consent because of sedative medication, a consultee will be sought (England and Wales) or a nearest relative/guardian or welfare attorney (Scotland). If this person is available in the hospital, is contactable, or is due to visit the patient within a reasonable timescale, then they will be provided with information about the trial and asked if they will provide written consent for the patient. This will be documented in the patient's notes.

2. Situations may arise in which the patient is sedated and there is no personal consultee (England and Wales) or nearest relative/guardian or welfare attorney (Scotland) or where this person is not contactable or able to visit the hospital at short-enough notice to be able to enrol the patient in a timely manner. In such cases we advocate enrolment would be possible with written agreement from a nominated consultee (England and Wales) or a welfare attorney (Scotland) as defined in the Table. This will be documented in the patient's notes.

In emergency situations, a patient unable to consent for themselves may still be recruited into DISCUS without prior advice from a consultee. In England and Wales, the law allows patients who are otherwise eligible for DISCUS but not able to consent for themselves to be recruited without prior advice from a consultee, in emergency situations if the local team decide that:

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

In emergency situations, a registrar/consultant or equivalent neurosurgeon who does not have GCP certificate may obtain consent or consultee advice for DISCUS. It should be noted that there is no legal requirement for studies which are not clinical trials of investigational medicinal products to be conducted in accordance with the conditions and principles of GCP. However, it is still important that such research is always conducted in a manner that provides public assurance that the rights, safety

and wellbeing of research participants are protected and that research data are reliable. Members of the research team in such studies are expected to be qualified by education, training or experience but should not be required or expected to undertake GCP training.

RETROSPECTIVE CONSENT: Patients who entered DISCUS via proxy consent and who regain capacity whilst in hospital will be informed about the trial and retrospective consent to continue participation will be sought from them. If at any stage either the consultee or nearest relative/guardian or welfare attorney or the patient chooses to withhold consent, then the patient will be withdrawn from the trial. Any advance statement by the participant will be respected.

A PERSON NOT CONNECTED WITH THE CONDUCT OF THE TRIAL: For the purposes of the DISCUS trial, the following people are excluded from providing consent:

a) A person who undertakes activities connected with the management of the trial;
c) An investigator of the trial or;
d) A health care professional who is a member of the investigators delegated team for the purposes of the trial.

INFORMED CONSENT FORM: The Informed Consent/Consultee declaration forms must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator or designee must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation. The Informed Consent/Consultee declaration form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The investigator will retain the original of each participant signed informed consent form. QRI is an optional part of the study; a consent form and PIS (different from the ones used for the RCT or the mechanistic study) will be used for QRI and will mention that the patient may be contacted by QRI researchers (see 7.2.1).

NEW INFORMATION: Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial will be communicated to the participant as soon as possible, verbally if the participant is in hospital, or by post/email if they have been discharged. We do not anticipate any such information.

7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

CONSENT FOR MONITORING FROM INJURY SITE: Patients who, in addition to the main RCT, are also recruited into the mechanistic study (i.e. insertion of probes to monitor from the injury site) will receive additional information regarding these monitoring studies including on the PIS. The signed consent form will require the consenting person to indicate whether the patient has consented only for the clinical study or for both the clinical study plus injury site monitoring study. MD specimens will be analysed on site for standard metabolites (glucose, lactate, pyruvate, glutamate, glycerol). These samples will be stored on site and periodically shipped (anonymously) to Dr. Saadoun at City St. George's for further assay of cytokines. MD samples are not human tissue as they are fluid collected through a 20 kDa MD dialysis membrane; the MD samples thus only contain fluid molecules <20 kDa in size.

CONSENT FOR QRI: The QRI involves inviting patients to take part in an audio-recording of their recruitment discussion and/or take part in an interview about their experience of being invited to join the study. Prior to discussion of DISCUS, written consent may be sought from patients/their legal representative to audio-record the recruitment discussion and/or take part in an interview with the QRI

researcher as part of the integrated qualitative research. Patients will be able to consent to the audio recording and/or interview and decline participation in DISCUS or vice versa, decline the audio recording and/or interview but consent to participation in DISCUS. A separate consent form will record consent to take part in the integrated qualitative research.

7.3 The randomisation scheme

Once the patient has been identified as eligible, invited to take part and given their consent (except in emergency)/had consent provided by consultee or nearest relative/guardian or welfare attorney, participants will be randomised by a member of the research team on the site delegation log authorised to do so. We recommend that randomisation is done just before the surgery to minimise patient withdrawal post-randomisation.
Participants will be randomly allocated to the treatment options using a web based secure randomisation system (RRAMP) provided by the Oxford Clinical Trials Research Unit (OCTRU). Randomisation allocation will be implemented using a minimisation algorithm with the following minimisation factors:

1) Age group (<40, 40-60, >60 years)
2) Country (England, Wales, Scotland, Northern Ireland, plus others if International centres participate and randomise patients to the study).

The minimisation algorithm will be seeded with a number of allocations and a non-deterministic probabilistic element will be introduced in order to prevent predictability of the treatment allocation.

The participant's identifiable information – participant initials, sex, age, hospital number (medical record number), centre, will be recorded on the REDCap screening form which feeds into the randomisation form for randomisation on RRAMP, and will be uploaded to an encrypted, separate database at the University of Oxford. Name, date of birth, email, address, telephone number will be recorded in contact details for patient reported outcome collection by central team. These and the NHS number (CHI number in Scotland) collected will facilitate identification of patients at rehabilitation centres for follow up. Hospital number (or medical record number (MRN)) facilitates the identification of an emergency setting patient. Ethnicity will be collected at baseline. This information will be encrypted in REDCap with access of only trial administration at SITU.

7.3.1 Method of implementing the randomisation/allocation sequence

The allocation lists will be generated by the trial statistician and uploaded for use in the RRAMP system. Full details of the randomisation blinding plan and schedules will be documented and stored in the confidential statistical section of the eTMF.

7.4 Blinding

The patients and the assessors of primary and secondary outcomes (trained physiotherapists, rehabilitation doctors) will be blinded to trial treatment arm. Baseline AMS is assessed at presentation, prior to randomisation. When randomised, the patient will not be informed which trial arm they have been allocated to. At around 2 – 3 months post-surgery patients are transferred from the MTC, where the surgery was done, to a spinal injuries unit for rehabilitation. The 6 months post-randomisation assessment will be performed by a physiotherapist or rehabilitation doctor based at the spinal injuries unit, on a different site from the MTC where the surgery was done, that has no access to the notes from the original hospital other than, in some cases, the transfer letter.

We intend to instruct surgeons and physiotherapists, in the initial site visit, to state that the patient was part of the DISCUS trial, but not state details of the surgery that was performed.

We are confident that the physiotherapist or clinician that performs the 6-month assessment will not seek to un-blind themselves by seeking details from the MTC about the type of surgery that was performed. It is unlikely that the assessor becomes accidentally unblinded; in this case, the assessor will state the unblinding and the data will still be used. The study will report the number of unblinded assessments that have been performed.

7.5 Emergency Unblinding

Though this is applicable to drug trials, we do not foresee any situation that a patient recruited into DISCUS will require emergency unblinding.

7.6 Data to be recorded

All patients will have a medical history taken and a clinical examination as part of the routine standard care. The following are to be recorded in part I of the case report form (CRF):

ELIGIBILITY DETAILS:

1) Numbers screened, eligible, approached and recruited to the trial and all reasons for not being eligible, approached or recruited.
2) Informed consent process
3) Obtained consent or authorisation for enrolment

PATIENT DETAILS:

4) Patient demographics (ethnicity)
5) Co-morbidity at baseline according to the Charlson Index [Charlson et al., 1987].
6) Methylprednisolone administration

INJURY DETAILS:

7) Injury details (Date / time, Mechanism (road traffic accident, assault, fall, sport, other), Spinal level (C1-T1), upload ISNCSCI chart)
8) Pre-operative status (Heart rate, blood pressure, list other injuries)
9) Imaging review (MRI + CT). Note CT is done before the patient has entered DISCUS as part of standard of care; DISCUS does not request for this CT to be done but, if the scan is available, then DISCUS will use some information from this scan

The following details will also be recorded:

SURGERY DETAILS:

10) Surgery (Date / time, Approach: Posterior versus anterior+posterior, No. of levels laminectomised, Make of Duroplasty, Length / width of duroplasty patch (cm), Duration of surgery (minutes skin to skin), Estimated blood loss during surgery, American Society of Anaesthesiologist (ASA) grade

MECHANISTIC STUDY:

11) Pressure probe: Date inserted, date removed
12) Microdialysis probe: Date inserted, date removed
13) Hourly ISP, MAP, MD (glucose, lactate, pyruvate, glutamate, glycerol)
14) Recording and daily upload of hourly pressure probe readings – for 5 days post operation
15) Recording and daily upload of hourly microdialysis readings – for 5 days post operation
16) Cytokine assay results

POSTOPERATIVE (for up to two weeks after surgery):

17) List of operations for other injuries
18) ICU: no. of days stay

19) Imaging review (MRI)
20) CSF: CSF leak (yes/no), Pseudomeningocele (yes/no), lumbar drain (date inserted, date removed), re-operation for CSF leak (yes/no)
21) Pressure ulcers (yes/no)

SPINAL INJURIES UNIT (REHABILITATION):

22) Date of transfer to Spinal Injuries Unit
23) Date of Discharge from Spinal Injuries Unit
24) Name and address of rehabilitation centre

7.7 Trial assessments

Clinical assessments: Patients are admitted to neurosurgery units in MTCs where initial investigations, management and assessments are made. Screening against the eligibility criteria and approach for recruitment into DISCUS will be from an appropriate professional (e.g. neurosurgery or ICU specialist trainee, neurosurgery or ICU consultant, nurse, physiotherapist). Most importantly, for the computation of the primary outcome measure (ΔAMS) is completion of the AIS chart, which is routinely done in these patients at baseline (by physiotherapist, intensivist or neurosurgeon) and 6 months (physiotherapist or rehabilitation doctor). The ISNCSCI is standard and widely used. CUE-Q tests upper limb function, a dynamometer will be used to quantify grip strength, WISCI-II assesses walking ability and SCIM-III evaluates self-care and daily living including sphincter function and are all validated and routinely performed in TSCI patients by physiotherapists or rehabilitation doctors at spinal injury units. For a detailed description of these assessments, see the Spinal Cord Injury Research Evidence website [SCIRE Professional, 2016].

HRQoL assessments: The HRQoL assessments at 6 and 12 months will be sent to participants either by email or completed by telephone call from SITU, depending on patient preference. These assessments are valid to be administered by phone.

The schedule of trial assessments and methods for data collection is described in Table 1, below:

TIMEPOINT	DATA	DATA COLLECTION METHOD
Baseline	• Patient characteristics • AIS (motor, light touch, pinprick, grade) • MRI scan • CT scan	• AIS completed by neurosurgeon, intensivist, physiotherapist • NIHR research nurse/local clinical team
Surgery within 72 hours of TSCI		
1-14 days post-operative	• Reoperations including procedure specific complications • Serious adverse events • MRI: compressed cord length, size of pseudomeningocele • Samples for mechanistic study if participating	• NIHR research nurse/local clinical team • P.I. neuroradiologist • MD samples • Reported SAEs and listed procedure-specific complications

6 months from randomisation	• AIS (motor, light touch, pinprick, grade) • HRQoL (SF-36) • CUE-Q, WISCI-II, SCIM-III, grip strength • Length of hospital stay • Re-operations on spine including procedure specific complications • MRI: cord tether, syrinx, spinal deformity, size of pseudomeningocele • Serious adverse events	• HRQoLcompletion, patient/carer will self-complete in clinic or via email/ phone call or by post • AIS, CUE-Q, WISCI-II and SCIM-III assessments completed by physiotherapist, rehabilitation doctor • NIHR research nurse/local clinical team • P.I. neuroradiologist
12 months from randomisation	• HRQoL (SF-36) • Mortality • Reoperations (including procedure specific complications) • Serious adverse events	• Completion via email or by phone call or by post, from hospital notes or from GP. • Reported SAEs and listed procedure-specific complications

Imaging assessments: MRI and CT images will be transferred by image exchange portal (IEP) or otherwise to St. George's Hospital for analysis. The preoperative CT is done **before the patient has entered DISCUS** as part of standard of care. DISCUS does not request for this CT to be done but, if the scan is available as standard of care, then DISCUS will use some information from this scan. IEP is a web-based application that allows healthcare professionals to securely transfer patient images from one hospital to another. NHS and private hospitals have been using IEP since January 2010. Transfer of images by IEP is the preferred method of image transfer rather than CD to maximise data protection and improve patient management by ensuring the images are from the PACS (Picture Archiving and Communication System) of the source hospital to the PACS of the destination hospital. PACS is the standard medical imaging technology used to securely store and digitally transmit electronic images and clinically relevant reports that eliminates the need to manually file and store, retrieve and send sensitive information, films and reports. Pre-operatively, we will record cause of injury, level of injury, surgical approach and type of injury (as per AO sub-axial classification system A, B, C, F to be done by the neuroradiology P.I. based on CT). From the MRI done within 2 weeks of surgery, we will note how well the cord is decompressed i.e. the length of cord on T2 mid-sagittal view without CSF in front and behind it as well as size of pseudomeningocele. We will measure the cranio-caudal (height), antero-posterior (length) and medio-lateral (width) lengths of the pseudomeningocele using the T2 sagittal and axial MRI sequences, and estimate its volume as (height x width x length / 2). It is vital to record MRI features at 6 months including cord tethering (i.e. whether there is CSF around the cord) to the surrounding dura which is expected to reduce with duroplasty as more space is created around the cord as well as size of pseudomeningocele to be determined as described above.

A major problem with TSCI patients is delayed syrinx formation and therefore the size of syrinx (cranio-caudal length on T2) will also be assessed using the 6 month MRI. Finally, we will assess deformity at 6 months to make sure that duroplasty does not lead to kyphosis.

Assessment of complications: Complications will be recorded post-operatively and at clinic visits and will monitored and reported by the sites. We will record at 6 and 12 months the number of re-operations on the spine to ensure that duroplasty does not lead to further operations related to CSF leak or wound infection, though based on known safety data, we think this is unlikely. We will also record the length of hospital stay, which may reduce if duroplasty is beneficial, but may be confounded by availability of rehabilitation beds. Adverse events and complications relating to surgery will be recorded and reported by the sites.

Mechanistic assessments: From the monitoring to be performed for up to 5 days after surgery, we will assess mean daily ISP, SCPP, glucose, lactate, pyruvate, LPR, glutamate and glycerol. As there is no

consensus or evidence on what are considered normal ISP/SCPP/metabolite values, it is not ethical to alter treatment based on these values.

We will explain this to PIs during site visits and in the training videos. Once metabolites have been measured on site, the MD vials will be coded by patient number and day from injury and stored at -20 ^{0}C and periodically shipped to Dr. Saadoun at City St. George's, University of London for analysis of inflammatory markers to compute mean daily GROα, IL1α, IL1β, IL4, IL8, IL10, IP10, MCP1, MIP1α and MIP1β.

7.8 Long term follow-up assessments

Patients will be followed up for 12 months post-randomisation as part of the trial. As part of the consent process, participants will be asked to provide consent for longer-term follow-up through routine data collection methods such as Hospital Episode Statistics (HES) data

7.9 Integrated qualitative research

We recognise this trial may face challenges to successful recruitment and consent processes: the pool of eligible patients is relatively small (9 – 13 patients per year per centre); recruitment will be led by busy neurosurgical specialist trainees who may not prioritise trial recruitment in high-pressure surgical environments; consent may be by proxy at a stressful time for family members; and there may be issues with equipoise if surgeons, patients or families favour the novel procedure (decompression and duroplasty) over standard procedures. Unforeseen issues may arise when the trial is rolled out from the initial centres to the remaining MTCs in the main trial.

Given these challenges, we will integrate a QuinteT Recruitment Intervention (QRI) [Clark et al., 2013; Donovan et al., 2016] within the initial 9 month recruitment phase and during the first 15 months of recruitment to the main trial. The QRI has been integrated into more than 30 trials, identified as challenging for recruitment, including trials evaluating surgical interventions [Clark, 2013; ICP2019; Donovan et al., 2016]. There is observational evidence of the benefits associated with a QRI in at least five RCTs [Rooshenas et al., 2019b]. The QRI is a two-stage intervention to identify then address recruitment and consent challenges:

Phase 1: understanding recruitment: A multi-faceted, flexible approach using rapid triangulation of the following data [Rooshenas et al., 2019a] will investigate site-specific or wider recruitment obstacles in at least 4 initial sites, purposively sampled to reflect a range of practice in recruitment;

1) Review of wording of the PIS, patient video and consent forms to minimise information that may be unclear or misleading.
2) Mapping of eligibility and recruitment pathways across centres, including numbers of patients screened, identified as eligible, approached and recruited to identify points in the patient pathway where patients are 'lost' to recruitment [Wilson et al., 2018] and reasons why.
3) Audio-recording of trial recruitment discussions with patient/family member consent. Audio-recorded data will be analysed to identify recruiter best practice for information provision and content for training of recruiters across all sites.
4) In-depth interviews with i) members of the Trial Management Group (n = 3 – 6) ii) surgeons, nurses and others involved in trial recruitment (n = 10 – 20) iii) eligible patients (or their family members) who have been approached about trial participation, including those accepting and those declining participation in DISCUS (n = 10 – 20). Interviews provide insights into presentation of trial information, differences in application across clinical centres and insights into recruitment barriers.

5) Observation of TMG/TSC meetings to identify issues arising during the trial that could impact on recruitment.

Interviews with healthcare professionals, patients and consultees/relatives/welfare attorneys will be guided by screening log data and use purposeful sampling to include healthcare professionals, patients and next of kin from trial sites that are showing contrasting patterns of recruitment (i.e. including sites showing rapid and sites showing slower recruitment) in order to investigate the reasons for these contrasting patterns. Interviews with patients and next of kin will purposefully sample those approached at higher and lower recruiting sites and include those accepting and declining participation in DISCUS to explore reasons underlying decisions to take part or not.

Phase 2: Feedback to the Chief Investigator (CI) / Trial Steering Committee (TSC) and plan of action. The QRI researcher will present summaries of anonymised findings from phase 1 to the trial CI (and TSC, if agreed by the CI), identifying factors that appear to be hindering recruitment with supporting evidence. A plan of action will be drawn up to improve recruitment. It is likely that some aspects of the plan will be generic, such as techniques to explore patient preferences whilst others will be specific to DISCUS, individual sites or recruiters and training will be tailored accordingly and delivered via investigator/recruiter meetings or in 1:1 feedback with recruiters as appropriate.

The QRI has been presented as two distinct stages for clarity. In reality, these will overlap and will be conducted iteratively during months 7 – 30 of the trial (month 15 of stop-go assessment, then a further 15 months during which more centres will be opened). Findings from early recruiting centres in the stop-go phase will inform site initiation training of later opening of main phase centres. New avenues of enquiry will continue throughout the conduct of the QRI, particularly as large numbers of new centres are opened in the first year of the main phase (months 16 – 27). Rigorous analysis of screening log data for individual centres before/after interventions will be used to direct further investigation and/or training.

7.10 Withdrawal criteria

Participants in DISCUS may be withdrawn from treatment for the following reasons:

1) Following consent, but prior to surgery, a patient clinically deteriorates such that surgery is no longer considered in the patient's best interests.
2) Following consent, but prior to surgery, surgery is postponed beyond the 72-hour window.
3) During surgery, where the surgeon considers use of duroplasty is not appropriate or possible.

Where a participant withdraws from treatment they will continue to be followed-up unless they also withdraw from follow-up. Participants may be withdrawn from follow-up for the following reasons, if the participant has not received treatment by the time of withdrawal takes place for this reason then they will also be withdrawn from treatment:

4) During surgery, where the surgeon discovers that the dura is substantially damaged by the penetrating injury (e.g., stab injury)
   Note: This includes participants with a dural tear due to TSCI from penetrating injury (e.g., stab injury) only. Participants with other types of dural damage such as small perforations from bone fragments or caused accidentally by the surgeon during surgery can continue in the study though they may be unable to receive their allocated treatment.
5) A patient declines to continue participation in the trial.

In 1 – 5, the patient will receive standard of care treatment.

Given the nature of the primary outcome (assessment of motor function) and the planned study length, no formal interim analyses with stopping guidelines are planned. However, should surgical complications / adverse events above that typically expected be reported, these will be reviewed by the Data Safety and Monitoring Committee (DSMC).

Each patient has the right to discontinue their participation in the DISCUS trial at any time. If an unconscious patient regains capacity and makes a request to be withdrawn from the trial, then this will be accepted. Incapacitated patients may also be withdrawn from the trial if the consultee requests withdrawal. In addition, the investigator may withdraw the patient from their allocated treatment arm if, subsequent to randomisation, a clinical reason for not providing the allocated treatment is discovered.

As the trial is on an intention to treat basis, any data collected will remain in the trial and the patient will continue to be followed up unless consent to continue data collection has been withdrawn.

Initially patients who have been withdrawn from the trial will not be replaced as the power calculation for the trial allows for a 15 % loss to follow up, however the withdrawal rate will be monitored and patient replacement will be at the discretion of the Trial Steering Committee (TSC) should it exceed 15 %. All discontinuations and withdrawals will be documented in the CRF. If a patient wishes to discontinue, anonymised data collected up until that point will be included in the analysis.

7.11 Loss to follow-up

Loss to follow up is defined as no response received in 3 consecutive separate attempts to contact a participant. Loss to follow-up is expected to be low but, at discharge from recruiting centre a family member/friend will be identified who can be contacted if the participant is too sick to respond to the questionnaires. The primary outcome, measured at 6 months, falls within the period that patients are still inpatients within spinal cord injury units, which further minimises loss to follow-up.

7.12 Storage and analysis of clinical (biological) samples

ONSITE ANALYSIS OF MD SAMPLES. MD is widely used for the management of patients with traumatic brain injury in ICU. The MD catheter, infusion pump, solutions, analyser and overall setup are the same for TSCI. A key component of MD is the catheter, which is used to sample molecules from extracellular space. The tip of the catheter in contact with the cord comprises a length of tubular dialysis membrane through which an artificial perfusion solution devoid of the molecules of interest, is constantly perfused. The dialysis membrane is semipermeable and permits free transport of molecules found in the extracellular fluid that are <20,000 Da in size. The MD sample is a microdialysate i.e. it contains no cells and is not a tissue. The MD fluid is collected in standard MD vials hourly and periodically analysed in a bedside analyser found in ICU. At least 50 patients (25 per arm), will have MD monitoring; tissue metabolite data (i.e. glucose, lactate, pyruvate, glutamate, glycerol and LPR) will be obtained on site using a MD analyser. Since the levels of monitored parameters may be confounded by time from injury, analysis will compare corresponding daily averaged values in the laminectomy versus laminectomy + duroplasty arms.

ANALYSIS OF CYTOKINES FROM MD SAMPLES: We hypothesise that duroplasty reduces cord inflammation and thus predict lower levels of pro-inflammatory cytokines in the duroplasty *versus* non-duroplasty arms. A poorly understood phenomenon after spinal cord injury is syrinx that causes delayed neurological deterioration. Because IL1α, IL1β, GROα, MCP1, MIP1α and MIP1β play key roles in syrinx formation, we hypothesise that by reducing cord inflammation, duroplasty will also reduce syrinx size (quantified from MRI at 6 months). We chose these cytokines because they are <20 kDa (i.e. cross the MD membrane) and play a key role in TSCI and syrinx formation (Table).

CYTOKINE	INFLAM-MATORY	ROLE IN SCI	Coefficient of variation %
IL1α	+	*J Neurosci.* 2015;35:10715. IL1α deletion protects oligodendrocytes after SCI. *J Neuroinflam.* 2012;9:65. IL1α activates microglia/macrophages in SCI. *J Neurotrauma.* 2012;29:1838-49. IL1α contributes to syrinx formation.	16.5
IL1β	+	*Spine.* 2004;29:966. IL1β is upregulated in human SCI. *PNAS.* 2014;111:8263. IL1β may cause chronic pain after SCI. *J Neurotrauma.* 2012;29:1838-49. IL1β contributes to syrinx formation.	3.6
IL4	–	*J Neurosci Res.* 2010;88:2409. IL4 reduces syrinx formation after SCI. *Pharmaceuticals.* 2017;10(4). IL4 is neuroprotective after SCI.	7.3
IL8	+	*J Neurotrauma.* 2010;27:669-82. IL8 is upregulated in human SCI. *J Neurotrauma*. 2018;35:435. CSF IL8 predicts outcome after SCI.	2.2
IL10	–	*J Neuroinflam.* 2019;16:93. IL10 limits inflammation/improves outcome in SCI. *J Neurotrauma.* 2013;30:1311-24. IL10 is beneficial after SCI.	15.1
IP10	+	*J Neurosci Res.* 2006;84:724. Neutralizing IP10 reduces apoptosis and increases axon sprouting after SCI. *J Neurosci Res.* 2004;77:701. Neutralizing IP10 enhances tissue sparing and angiogenesis after SCI.	2.7
GROα	+	*J Cell Physiol.* 2012;227:1335-46. Increased GROα expression after SCI. *J Neurochem.* 2001;78:1064. GROα neutrophil chemoattraction in SCI. *J Neurotrauma.* 2012;29:1838. GROα contributes to syrinx formation.	5.5
MCP1	+	*J Neurotrauma.* 2010;27:669-82. MCP1 is upregulated in human SCI. *J Neurosci Res.* 2002;68:691-702. Monocyte recruitment & myelin removal delayed after SCI in mice with non-functional MCP1. *J Neurotrauma.* 2012;29:1838. MCP1 contributes to syrinx formation.	5.4
MIP1α	+	*J Neurosurg Spine.* 2011;14(5):583-97. Increased MIP1α expression after SCI. *J Neurotrauma.* 2012;29:1838. MIP1α contributes to syrinx formation.	14.3
MIP1β	+	*J Neurosci.* 2017;37(48):11731-11743. Increased MIP1β after SCI. *Spinal Cord.* 2017;55(11):1002-1009. Increased MIP1β after SCI. *J Neurotrauma.* 2012;29:1838. MIP1β contributes to syrinx formation.	4.5

We have an up-and-running multiplex ELISA and have a study in press in *Scientific Reports* showing that, in general, these cytokines are downregulated in TSCI after induced local hypothermia with rebound upregulation after rewarming. These cytokines are quantifiable from the microdialysis fluid with high reproducibility (low Coefficients of Variation). The cytokines may also shed light on the inflammatory pathways e.g. reduced cord inflammation (lower IL1α, IL1β, higher IL10), reduced neutrophil activation (lower GROα, IL8, MIP1α, MIP1β) reduced macrophage activation (lower IP10, MCP1), M2 macrophage polarisation (increased IL4) in the duroplasty arm. Leftover MD samples will be stored locally in a freezer and periodically shipped to Dr. Saadoun's team at City St. George's, for multiplex ELISA of cytokines (GROα, IL1α, IL1β, IL4, IL8, IL10, IP10, MCP1, MIP1α, MIP1β). These metabolites and cytokines are stable with freeze-thaw, for several hours at 25 ^{o}C and indefinitely at -20 ^{o}C; thus, measurements are independent of variability in sample collection. The stored vials will be anonymised for analysis and destroyed once the measurements have been made.

STAFF TRAINING: NICU staff will be trained not to intervene to treat ISP, SCPP and MD values, otherwise the two trial arms may receive different medical managements. ICU nurses are accustomed to collecting and analysing hourly microdialysate vials. Each vial contains ~18 μL fluid and is assayed in a bedside analyser for glucose, lactate, pyruvate, glutamate and glycerol. There is ~10 μL sample left over in each vial after this analysis, i.e. for each patient there will be ~10 x 24 = 240 μL leftover MD sample per day for up to 5 days. We propose using these leftover samples (pooled daily) to assay for these cytokines. Thus, the cytokine assay does not require additional procedures on patients.

7.13 End of trial Participation

The date that all data has been collected and cleaned from all trial participants.

8 TRIAL TREATMENTS

DUROPLASTY: All patients will undergo surgery that involves spinal fixation and bony decompression including laminectomy. The surgical approach (anterior *versus* posterior fixation, no. of levels) is at the discretion of the local clinicians as are the target physiological parameters during surgery (blood pressure, arterial CO_2, O_2 etc.). However, the study requires that patients also have laminectomy spanning the levels of swollen cord based on the MRI, which requires a posterior approach.

Patients randomised to the duroplasty arm will also undergo expansion duroplasty, dorsally, under the same general anaesthetic. Therefore, patients will undergo either a posterior approach only (lateral mass screw fixation + laminectomy +/- duroplasty) or combined anterior and posterior approach. In the latter case, the surgeon may elect to fix anteriorly and posteriorly (so called 360-degree fixation) or only fix anteriorly and perform laminectomy +/- duroplasty posteriorly without additional fixation.

We recommend that a wound drain be placed on gravity and the skin be sutured and covered with waterproof adhesive film dressing e.g. IOBAN, an iodine impregnated dressing that minimises the risk of wound infection and of CSF leak. The wound drain and dressing are normally removed at 1 week and the sutures at 2 weeks. CSF leak is normally treated by placing extra sutures or a lumbar drain. Though neurosurgeons are familiar with duroplasty, the technicalities of the procedure will be discussed at the initial site visit and by detailed online training modules. The length of the duroplasty will span the length of the swollen cord estimated from the preoperative MRI. Duroplasty will be performed by suturing an elliptical patch of artificial dura about 1 cm longer than the dural incision and about 2 cm wide to the dural edge [Phang et al., 2015].

MONITORING PROBES: The patients for the mechanistic studies will also have a pressure probe and/or a MD catheter inserted intradurally posteriorly at the site of injury for up to 5 days and removed in ICU. Probe insertion is done at the time of surgery to fix the spine. Each probe is tunnelled through the skin and soft tissue, inserted through the dura with the tip positioned at the site of maximum swelling [Werndle et al., 2014; Phang et al., 2016]. The technicalities of probe insertion, tunnelling, suturing to the skin and removal will be discussed at the initial site visit and by detailed online training.

9 COMPLICATIONS

9.1

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant. Note: An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the trial procedures, whether or not considered related to the procedures.
Adverse Reaction (AR)	All untoward and unintended responses related to a trial intervention/procedure.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: a) results in death b) is life-threatening c) requires inpatient hospitalisation or prolongation of existing hospitalisation d) results in persistent or significant disability/incapacity e) consists of a congenital anomaly or birth defect f) is otherwise considered medically significant by the Investigator Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the

	event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	This is a term used to describe a serious adverse response/reaction to a trial procedure/intervention, the nature or severity of which is not listed in the protocol or other applicable information as an expected event.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

9.2 Assessment of Causality

The relationship of each AE to the trial intervention will be determined by the investigator (or a delegate who is medically qualified and listed on the site delegation log) according to the following definitions:

Attribution (Causality)	**Description**
Unrelated	The AE is clearly NOT related to the intervention
Unlikely	The AE is doubtfully related to the intervention
Possible	The AE may be related to the intervention
Probable	The AE is likely related to the intervention
Definite	The AE is clearly related to the intervention

Once the SAE form is submitted to the CTU (Sponsor Representative), there will be a review of the SAE by the Trial Management Team, and any queries will be sent to the site for clarification. The assessment of causality by the investigator will not be downgraded by the CTU. A clinician unrelated to surgery may be consulted on the SAE assessment.

9.3 Operational definitions for (S)AEs

The following will be reported by site as an SAE reportable to the central team within 24 hours:

- Death: only if deemed potentially directly related to duroplasty or probes (for example meningitis from CSF leak).

- Meningitis (defined as fever + symptoms/signs of meningism + elevated CSF neutrophil count and positive CSF microbiology culture)

- Redo spinal surgery: only if deemed potentially directly related to duroplasty or probes (e.g. repair of CSF leak, removal of retained probe)
- Worsening of AIS grade: only if deemed potentially directly related to duroplasty or probes
- Wound infection that requires antibiotics: only if deemed potentially directly related to duroplasty or probes
- Wound breakdown that requires surgical debridement: only if deemed potentially directly related to duroplasty or probes (i.e. wound breakdown from deep infection)

EVENTS EXEMPT FROM BEING REPORTED AS SAEs

The following are complications and collected as outcome and do not require SAE reporting:

- Death: related to reasons other than duroplasty or probes *(e.g.: deaths related to pulmonary embolus)*
- Repair of CSF leak not requiring general anaesthetic *(e.g. Lumbar drain insertion, Re-suturing of wound of probe site)*
- Redo spinal surgery unrelated to duroplasty or probes *(e.g. evacuation of haematoma, surgery for: Metalwork failure, Deformity correction, Removal of metalwork, Syrinx)*
- Worsening of AIS grade (*If deemed NOT related to duroplasty or probes, this does not need reporting and will be picked up in 6-month ISNCSI/assessment)*
  ** Note: 5% of patients have unexplained worsening of AIS grade. **
- Deep wound infection that needs antibiotics if deemed NOT related to duroplasty or probes
- Wound breakdown that requires surgical debridement if deemed NOT related to duroplasty or probes
- Pseudomenigocele
- Pressure ulcers (during 1st week post op - outside this period no need to report)
- Readmissions to hospital

DISCUS collects all complications (adverse events – events exempt from being reported as SAEs). The investigators are encouraged to report an event as an SAE if unsure and contact the trial office. Events collected as complications from sites will be reviewed by the TMG monthly and assessed by team of clinicians unrelated to surgery.

Assessment and management of risk

Where possible, SAEs and SARs will be evaluated for duration and intensity e.g.: Lumbar drain insertion to treat CSF leak (no. of days), Meningitis (duration of antibiotics), Redo spinal surgery (duration of hospital stay), Worsening of AIS grade (grade), Wound infection that requires antibiotics (duration of antibiotics), Wound breakdown that requires surgical debridement.

Breaking the blind will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical or surgical management of the participant. We do not anticipate that breaking of the blind will be required for DISCUS.

9.4 Recording and reporting of SAEs, SARs AND SUSARs

All SAEs occurring from the time of written informed consent/ randomisation until 12 months post randomisation should be recorded on the SAE Report Form. Trial centres will use a standardised electronic SAE form to inform the Trial Manager of SAEs. All SAEs (other than those defined in this protocol as not requiring reporting) must be reported on the SAE reporting form on REDCAP .

The Trial Management Team will perform an initial check of the report and request any additional information from the site team. SAEs will also be reviewed at TMG meetings. DSMC and TSC will get a list of SAEs.

The 'causality', 'expectedness' and 'seriousness' of SAEs (i.e. relationship to trial treatment) will be assessed by the local investigator(s) on the SAE form. A clinician unrelated to surgery may be consulted on the SAE assessment. All SAEs, will be reviewed by the DISCUS Trial Manager and discussed with Chief Investigators to determine whether the SAE is "*related"* and "*unexpected"* as defined by the HRA guidance. These will then be assessed by the DISCUS Nominated Person.

The assessment of 'causality' by the local investigator will not be downgraded by the DISCUS Trial Office, even if the Nominated Person does not concur with the assessment. Under these circumstances both assessments will be recorded and causality deemed as 'related'.

For SAEs that require reporting, expectedness of SARs will be performed centrally by the Nominated Person for the trial and determined according to the Sponsor-.

The DISCUS Trial Office is responsible for reporting SAEs, where appropriate, to the Sponsor and REC within required timelines. An SAE occurring to a participant will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigators the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures.

All SUSARs (Suspected and Unexpected Serious Adverse Reaction – a serious adverse reaction, the nature and severity of which is not consistent with the information documented about the procedure or treatment in question) will be reported by the DISCUS Trial office to the relevant Competent Authority and other parties as applicable. For fatal and life-threatening SUSARs, this will be done no later than seven calendar days after the Sponsor or delegate (i.e. CTU) is first aware of the reaction. Any additional relevant information will be reported within eight calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

For each **SAEs/SUSARs** the following information will be collected:

a) full details in medical terms and case description
b) event duration (start and end dates, if applicable)
c) action taken
d) outcome
e) seriousness criteria
f) causality (i.e. relatedness to trial treatment), in the opinion of the investigator

Any change of condition or other follow-up information should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached."
OCTRU safety reporting procedures will be followed at all times.

Management in the event of withdrawal
Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study, at any time, if they consider it necessary for any reason.

Participants in DISCUS may be withdrawn from treatment if:

1. Following consent, but prior to surgery, a patient clinically deteriorates such that surgery is no longer considered in the patient's best interests.

2. Following consent, but prior to surgery, surgery is postponed beyond the 72-hour window.

3. During surgery, where the surgeon considers use of duroplasty is not appropriate or possible.

Where a participant withdraws from treatment they will continue to be followed-up unless they also withdraw from follow-up. Participants may be withdrawn from follow-up for the following reasons, if the participant has not received treatment by the time of withdrawal takes place for this reason then they will also be withdrawn from treatment:

4. During surgery, where the surgeon discovers that the dura is substantially damaged by the penetrating injury (e.g., stab injury)

5. A patient declines to continue participation in the trial.

Participants that withdraw from follow-up will be asked whether the data acquired up to the point of withdrawal can be retained. The reason for withdrawal will be recorded in the participant's medical records and in the DISCUS Withdrawal Case Report Form (CRF). If the participant is withdrawn due to a SAE, the local investigator will arrange for follow-up visits until the SAE has resolved or stabilised.

Members of the trial team will explain to participants the value of continuing to complete questionnaires and participate in assessments at follow-up. Where possible, participants who have withdrawn from the trial intervention should continue to be followed up, unless they withdraw consent for this.

9.5 Responsibilities

Principal Investigator (PI):
Checking for SAE's when participants attend for treatment / follow-up.

- Using medical judgement in assigning seriousness and causality and providing an opinion on whether the event/reaction was anticipated.
- Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that SAEs are recorded and reported to the sponsor in line with the requirements of the protocol.

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

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning whether and event/reaction was anticipated or expectedness.
4. Immediate review of all SUSARs.
5. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs

Sponsor: (NB where relevant these can be delegated to CI)

7. Central data collection and verification of SAEs and SUSARs according to the trial protocol onto a database.
8. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
9. Reporting safety information to the independent oversight committees identified for the trial (Data Safety and Monitoring Committee (DSMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
10. Expedited reporting of SUSARs to the REC within required timelines.
11. Notifying Investigators of SUSARs that occur within the trial.
12. The unblinding of an assessor for the purpose of expedited SUSAR reporting [For double blind trials only].

Trial Steering Committee (TSC):
In accordance with the TSC charter (filed in the trial eTMF), periodically reviewing safety data and liaising with the DSMC regarding safety issues.

Data Safety Monitoring Committee (DSMC):
In accordance with the DSMC charter (filed in the trial eTMF), periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The sample size is based on the primary outcome of change in AMS score from baseline to 6 months. Assuming a 6-month improvement in ΔAMS from a mean(SD) of 17(25) in the control arm to 28(25) in the intervention arm, allowing for 15 % patient loss to follow-up by 6 months (including patient death which is estimated to be around 2-3 % by 6 months), a total sample size of 222 patients is required with statistical power of 85 % and 2-sided significance level of 5 %. The assumed difference in ΔAMS and SD are based on our exploratory study [Phang et al., 2015] and are supported by data from the EMSCI database and other published series [Fehlings et al., 2016; WU et al., 2015] in which ΔAMS is between 15 – 18 with SD ranging from 15 – 25. There is expected correlation between the baseline and 6-month AMS scores, however there is no robust data on the strength of the correlation for patients with severe TSCI and thus we are unable to accurately account for this in the sample size calculation. By assuming no correlation, with the expectation that correlation is observed in the data, statistical power to detect a difference between the two treatment arms will be increased.

The threshold difference in ΔAMS between the two trial arms of 11 points is comparable to other RCTs for cervical TSCI, for example the RISCIS study was powered to detect a 9-point difference between treatment arms [Fehlings et al., 2016]. The minimal clinically important difference in AMS remains controversial and there is no clear consensus amongst the clinical community [Wu et al., 2015]. This is mainly because the segmental distribution of any increased AMS score is functionally more important than the absolute value of the change, e.g. a ΔAMS in hand muscles is functionally more important than the same change distributed over many muscle groups. Based on our discussions with patients and international experts, for a low cost, low risk treatment such as duroplasty, any improvement in motor function would be considered beneficial. We will use functional scales as secondary outcomes including CUE-Q (hand function), grip strength, WISCI II (walking) and SCIM III (independence measure that includes sphincter function and validated in TSCI) to confirm that the motor improvement that we seek is associated with functional improvements. In addition, we use a HRQoL scale as a secondary outcome measure (SF-36) aiming to show that the functional improvement translates to improvement in HRQoL.

For a UK-only recruitment, we will maintain statistical power of 85% power, requiring 222 participants. However, as this will be the definitive trial to address the research question, we will aim to increase the statistical power from 85 to 90%, increasing total recruitment from 222 to 260 participants, depending on recruitment rate. Whilst recruitment is in progress, the statistical power will be revised from 85 to 90% if it becomes clear that non-UK centres will secure funding to recruit patients to the study and that the new recruitment figure is achievable within the current recruitment duration. Recruitment progress will be monitored by the TMG and TSC and the final decision to increase recruitment will be made by the TSC.
MECHANISTIC STUDY: Since the proposed mechanistic studies are intended to be hypothesis-generating, no formal sample size calculation has been performed. We consider recruitment of $n \geq 50$ is achievable for UK centres and, if International centres participate, the number is likely to rise. These studies are an important component that will provide information on the mechanism of action of duroplasty. We predict that, compared with bony decompression alone, bony decompression with duroplasty will better decompress the cord (reduce ISP) thus improve cord perfusion (increase SCPP). Improved cord perfusion is predicted to increase cord glucose (and oxygen), which will reduce cord anaerobic metabolism (lower lactate, lower LPR), reduce excitotoxicity (lower glutamate) and reduce cell death (lower glycerol).

All NICUs have the ability to monitor pressure from injured brain (ICP) and the equipment required for ISP monitoring for TSCI is the same. However, only a few NICUs monitor MD. Many NICUs are keen to contribute patients for the RCT, but do not wish to monitor from the injury site. Given these constraints, we elected, following discussions at the Duroplasty meeting in 2018 and in the ICP2019 meeting to have injury site monitoring as an optional extra so not to discourage sites who would otherwise have participated in patient recruitment. Of the injury site monitoring, some units will only do ISP monitoring and others both ISP monitoring and MD monitoring. At St. George's NICU we have a setup for injury site monitoring including ISP [Werndle et al., 2014] and MD [Phang et al., 2015] and Addenbrooke's NICU has a setup for brain. We estimate that St. George's and Cambridge will enter most of their recruited patients into the mechanistic study. Several other units also wish to contribute patients into the mechanistic study (as indicated at the Duroplasty 2018 meeting, the ICP2019 meeting and Table 4); thus, the number of patients recruited into the mechanistic study may exceed 50. We have received letters of interest from 22 centres for ISP monitoring and 15 centres for MD. The consumables have been costed, but any equipment is up to each unit to purchase.

All neurosurgical units have equipment to monitor pressure as it is routinely used for TBI; the same can be used for ISP monitoring. MD equipment is only available in some neurosurgery units. DISCUS

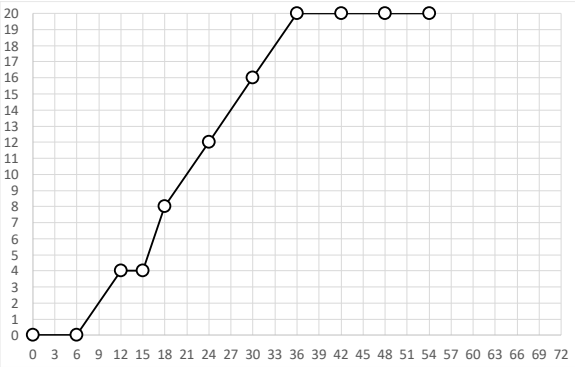
will cover costs of consumables (e.g. ISP probes, MD catheters, MD solutions) but will not cover costs of purchasing monitoring equipment.

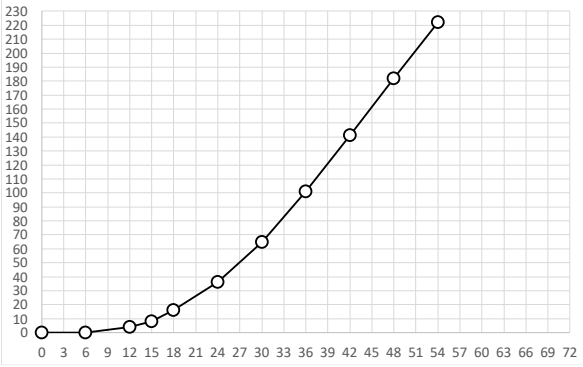
10.2 Planned recruitment rate

Based on recruiting 222 participants:

1) Recruitment starts at month 7 of the project.
2) Recruitment at 20 centres.
3) Each centre needs 3 months initial approvals period before starting recruitment.
4) 4 new centres join per 6 months starting at month 7.
5) Mean number of eligible patients per centre per month = 0.84 – 1.07 patients.
6) Each centre recruits only 33 % of eligible patients.
7) Assumes maximum of 20 recruiting centres

Below is the predicted total no. of (*left*) recruiting centres and (*right*) recruited patients *versus* end of month counted from start of study (85% power).





10.3 Statistical analysis plan

This section provides a brief summary of the statistical analysis with full details being included in a separate statistical analysis plan (SAP). Full details of the statistical analysis will be detailed, in advance of un-blinding of the data, in a pre-specified SAP. The SAP will be written in accordance with the current OCTRU SOPs and will be agreed by the study statistician, the CI and the TMG.

10.3.1 Summary of baseline data and flow of patients

The baseline comparability of the two intervention groups will be considered. The intervention groups will be compared in terms of minimisation factors, demographic characteristics and outcome measures at baseline. Numbers (with percentages) for binary and categorical variables and means (with standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented; there will be no tests of statistical significance nor confidence intervals for differences between the randomised groups on any baseline variable.

A consort diagram will be produced prior to publication according to the consort statement guidelines.

10.3.2 Primary outcome analysis

The primary analysis will be performed according to the intention-to-treat principle and will be analysed at a 2-sided 5% significance level. The primary outcome, change in AMS score from baseline to 6 months, will be analysed using a generalised estimating equation (GEE) model or mixed model for repeating measures (MMRM) model (depending on the distribution of the primary outcome),

adjusted for randomised treatment and baseline AIS grade. Minimisation factors (age group, country) will be adjusted for as fixed effects. A secondary analysis will be performed adjusting for other important, pre-specified prognostic factors. The mean score and SD will be plotted at each time-point as a visual representation and will be summarised at baseline, 3 months and 6 months.

The AIS ISNCSCI assessment involves systematically completing the AIS form and, therefore, we do not anticipate missing values. Any missing date for the primary outcome (AMS) will be reviewed on a case-by-case basis by an independent clinician who is blinded to the treatment the patient received. AIS grade A or B patients have 0 motor score below the injury by definition and will thus be included in the primary analysis, whereas an AIS grade C patient cannot have missing motor scores and therefore, in the possible but unlikely scenario where values are missing, the AIS will be independently reviewed.

10.3.3 Secondary outcome analysis

MMRM will be used to evaluate difference over time by treatment group in HRQoL outcomes. MMRM models will be adjusted for minimisation factors, treatment, baseline score, visit and a treatment by visit interaction as fixed effects, with patient included as a random effect. Differences between treatment groups will be reported as mean differences with 95% confidence intervals. Absolute and percentage changes in HRQoL outcomes from baseline assessment will be displayed graphically. HRQoL forms that are returned partially complete will be analysed according to the scoring instructions for each questionnaire.
Binary outcomes will be assessed using chi-squared tests and logistic regression analyses, adjusting for baseline and minimisation factors. Normality will be assessed for continuous outcome measures and differences between treatment arms will be assessed using a t-test or Mann-Whitney U test and presented as mean differences with 95% confidence intervals or median differences with interquartile range. Linear regression or GEE models will be used to adjust for baseline, minimisation and other important prognostic factors.
Survival analysis methods will also be used to compare differences between the treatment groups for overall survival (OS). Time to OS will be displayed using Kaplan-Meier plots.
Absolute (death rates at 12 months) and relative differences (hazard ratios) will be reported together with 95% confidence intervals.

10.4 Subgroup analyses

Exploratory sub-group analyses will assess the impact of the minimisation factors under the treatment effect. Planned subgroup analyses will be specified in the SAP.

10.5 Interim analysis and criteria for the premature termination of the trial

No formal interim analyses are anticipated prior to completion of follow-up for the designated time points. The DSMC may request interim analyses at any point in the trial, which will be performed by the trial statistician. A DSMC charter will be in place for the DISCUS trial.

10.6 Participant population

The primary analysis population will be all randomised patients.

10.7 Procedure(s) to account for missing or spurious data

The number and percentage of individuals with missing data for each outcome at each time point will be summarised by intervention arm, along with reasons for missing-ness if known. The pattern of missing-ness will also be explored and the suitability of missing data assumptions considered.

The main analyses of the primary and secondary outcomes in this trial will be performed using the available case dataset. The impact of missing data on the results of the analysis of the primary outcome at the primary time point will be investigated. Missing data for the primary outcome is expected to be minimal (see 'Primary Outcome Analysis' section).

10.8 Economic evaluation

No economic evaluation is planned.

10.9 QRI data handling and analysis

All interviews will be audio-recorded, transcribed verbatim and edited to ensure anonymity of respondent. Data will be managed using NVivo software. Transcription will be undertaken by an approved transcription service/transcriber that has signed the necessary confidentiality agreements with the University of Bristol. All transcripts will be edited to ensure anonymity of respondent. Data will be managed using NVivo software and stored on encrypted drives at the University of Bristol, in line with the university's data storage policies and current GDPR legislation.

Interview data will be analysed thematically using constant comparative approaches derived from Grounded Theory methodology [Strauss et al. 1994].

Audio-recorded recruitment consultations will be subjected to targeted transcription and subject to the same processes to ensure anonymity of participants as listed for interview data above. Transcripts will be subject to content, thematic, and novel analytical approaches, including targeted conversation analysis [Wade et al., 2009]and quanti-qual appointment timing (the 'Q-Qat method') [Paramasivan et al., 2015] as described in the QRI protocol [Donovan et al., 2016]. Triangulation across all these data will inform feedback to the DISCUS TMG (described in 7.9 above). De-identified quotes from interviews and audio-recorded recruitment consultations may be used in recruiter training within DISCUS and in publications.

At the end of the study, audio-recordings will be kept for at least 10 years before they will be destroyed. Transcripts will be stored indefinitely in secure research data storage designated 'controlled access', so can only be accessed by approved individuals who are interested in conducting their own analyses of the data. These individuals will have to submit an application to do this, which will be assessed by an independent committee. However, all data will have identifiable information removed before they are made available, and there will be no way to identify any individuals mentioned in interviews/appointments.

11 DATA MANAGEMENT

A Data Management and Sharing Plan (DMP) will be produced for the trial and will include reference to confidentiality, access and security arrangements. All data will be processed in accordance with data protection rules. Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

All trial data will be collected on trial specific documents, for example questionnaires and case report forms (CRFs). All trial-specific documents, except for the signed consent form and follow-up contact details, will refer to the participant with a unique study participant number/code and not by name. The participants will be identified by a participant ID number +/- year of birth on all study documents and any electronic database. Participant identifiable data will be stored separately from study data and in accordance with OCTRU SOPs. All trial data will be stored securely in offices only accessible by swipe

card by the central coordinating team staff in Oxford and authorised personnel. On completion of the study, and with appropriate participant consent, fully anonymised data may be shared with other organisations at the behest of the funder. All requests for the use of the data from the Discus study will be approved by the CI's and TMG. A data request form should be completed detailing the decision as to whether the request is accepted. In cases where individual site data is requested, only summary data would be provided with caveats for dissemination, to emphasise that trial data should be interpreted as a whole.

11.1 Data collection tools and source document identification

Source Data

For details on the questionnaires and assessments see Section 7.7 'Trial Assessments'. The data will be collected as follows:
Patient characteristics: These are in the patient notes kept either on paper or electronically at each hospital and then transferred to the trial database.
AIS: This is normally a standard paper chart completed on admission, on discharge from the MTC and at 6 months by the spinal injuries units and placed in the patient notes and then transferred to the trial database.
MRI and CT pre-op and MRI first 2 weeks post-op and MRI at 6 months: These are images normally stored electronically on each hospital's PACS and will be electronically transferred by IEP (which is a secure system used by UK NHS hospitals) to St. George's for further analysis by Dr. Ogungbeme.
Length of hospital stay, no. of re-operations on spine: This information will be obtained from hospital records and/or from the patient.
HRQoL: These are questionnaires that will be completed either online, on paper or by phone and transferred to the patient database.
CUE-Q, WISCI-II, SCIM-III: These are questionnaires that may require patient examination and the results will be kept in the patient records and transferred to the patient database.
Grip strength: This will be assessed using a dynamometer.
Complications and adverse events: These are recorded in patient notes and reported by each local investigator to the trial database.
Mortality: To be obtained from hospital records or reported by the local investigators or from the GP.

Case report forms

CRFs will not bear the participant's name, however their year of birth and trial ID will be used for identification and this will be clearly explained to the participant in the PIS.

CRFs as Source Documents

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the patient will be referred to by the trial number/code, +/- year of birth with no personal identifiable information.

QRI Data

QRI audio recordings and transcripts will be held on University of Bristol encrypted drives for a maximum of 10 years after the study ends.

QRI participants will be given the option to make transcripts of their data 'controlled access'. This means that transcripts will be stored in a secure online database for a minimum of 10 years. This database can be accessed by approved researchers who are interested in conducting their own

analyses of the data. These researchers will need to submit an application to do this, which will be assessed by an independent committee at the University of Bristol. All data will be de-identified before being made available.

11.2 Data handling and record keeping

The trial data (including data for SAE/AEs) will be entered onto a validated REDCap study database developed and maintained by OCTRU and which can only be accessed by authorised users via the REDCap application. The REDCap application resides on a webserver hosted and managed by Oxford University's Medical Services Division IT Services department (http://www.imsu.ox.ac.uk/). The server is on the university's backbone network and is backed up nightly to a secure off-site location. Consent will be obtained from the patients to be able to share information and prior to sharing, data will be anonymised. In addition, any indirect identifiers that may lead to deductive disclosures will be removed to reduce the risk of identification. After closure of the trial and data analyses, the data generated will remain the responsibility of City St. George's, University of London ("the contractor"). All requests for data should be directed to the contractor and managed by the contractor, in accordance with the City St. George's data sharing policies. Data access requests from a third party will be managed following the relevant policies and practices of City St. George's JRES and OCTRU. Release of data will be subject to a data use agreement between the contractor and the third party requesting the data. The data use agreement will detail the agreed use and appropriate management of the research data to be shared and include a requirement for recognition of the contribution of the researchers who generated the data and the original funder.

The contractor's policy and procedures for data access must include a dispute resolution process to resolve situations where the contractor and a third party requesting data disagree about data access. The TMF will be archived for 10 years from the end of the study.

Data will be captured on paper CRFs/worksheets and uploaded remotely by the site staff, as above, via a password into the web-based tool REDCap. Training on the use of REDCap will be provided to all site personal responsible for entering data and a copy of the REDCap guide will be available in the site file.

All completed paper worksheets will be kept in the Investigator Site File in patient packs. No CRFs will be sent to the trial office for uploading. The DISCUS trial office (based within SITU) will monitor the data and produce queries for sites to complete/resolve. The source data for 'clinical data' will be in the medical notes.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Delegation of Responsibilities Log will identify all trial personnel responsible for data collection, entry, handling and managing the database
All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which requires data to be anonymised as soon as it is practical to do so.

With regards to the HRQoL questionnaire (SF-36), a paper version is available for completion if participants are unwilling/unable to complete electronically; to then be entered centrally by the DISCUS trial staff.

Completion of these questionnaires will be centrally monitored by the DISCUS Trial office to assess rates of compliance and the completeness and quality of entered/received data.

Regarding Consent the details are checked following each randomisation against data stored in RRAMP. The database is designed to send an email to the DISCUS trial office informing them when a patient is randomised; which can only happen once consent has been taken. Confirmation of who took consent will be included in the email received by the DISCUS trial office and cross checked against the delegation log.

A copy of the signed ICF will be given to the participant and one copy will be placed in the participant's medical notes. The original signed ICF will be retained in the Investigator Site File (ISF).

Mechanistic study: ISP, MAP and MD measurements of metabolites will be recorded locally by the ICU nurses on patients' charts and entered onto the trial database as hourly measurements for up to 5 days after surgery. MD measurements of cytokines will also be recorded on anonymously and added to the trial database.

GCP requires that sponsors operating such systems validate the system, maintain SOPs for the use of the system, maintain an audit trail of data changes ensuring that there is no deletion of entered data, maintain a security system to protect against unauthorized access, maintain a list of the individuals authorized to make data changes, maintain adequate backup of the data, safeguard the blinding of the trial and archiving of any source data (i.e. hard copy and electronic). If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data. The sponsor should use an unambiguous participant identification code that allows identification of all the data reported for each participant. Sponsors are responsible for ensuring compliance with the requirements outlined above when tasks are subcontracted. There should be no loss of quality when an electronic system is used in place of a paper system.
Specific principles can be found here:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

11.4 Archiving

At the end of the trial, all essential documentation will be archived securely by the CI and trial sites for 10 years from the declaration of the end of trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.
Any associated trial documents in Oxford will be archived according to University of Oxford policy and this may include the use of an external professional archiving site.
The trial database and eTMF will be archived in accordance with OCTRU SOP GEN-048.
The trial database may be used in future studies to assess long term (e.g. 10 years) outcomes including incidence of syrinx formation in the two trial arms; separate approvals and funding will be required for such studies.

12 MONITORING, AUDIT & INSPECTION

A risk assessment will be undertaken (this will be filed in the DISCUS eTMF managed by SITU) and a proportionate monitoring plan will be put in place to decide on the extent and nature of any on-site

monitoring. Central monitoring of incoming data and operational aspects of the trial will be done by SITU according to a written plan. This will also be filed in the DISCUS eTMF managed by SITU. The non-UK sites are monitored by the International CTO: Medizinische Universität Innsbruck, Kompetenzzentrum für Klinische Studien (KSS), Anichstr. 35, A-6020 Innsbruck, Austria.

An independent DSMC will be established with an independent chair and suitable multi-disciplinary representation. The DSMC will meet annually.
The Chief Investigators will ensure that this trial is conducted in accordance with the current approved protocol, Good Clinical Practice, relevant regulations and OCTRU SOPs.
Triggered monitoring will be performed by SITU as determined by risk assessment and monitoring plan following GCP principles. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

13 ASSESSMENT AND MANAGEMENT OF RISK

13.1 General statement for all research

COVID-19 Risk Assessment and Management Strategy
DISCUS clinical and research staff are required to comply with their NHS Trust and University policies on COVID-19. For example, DISCUS staff who interact with patients may be required to complete an ongoing COVID-19 risk assessment prior to undertaking any work on their sites, which includes research activity. This process is continuously monitored by their responsible line manager.

Patients with TSCI (unaffected or affected by COVID-19) deemed to be high risk for COVID-19 or those patients in close contact with someone at risk may be recruited into DISCUS provided that the local clinical team have decided that the patient is fit to proceed with the spinal surgery. The decision whether to recruit TSCI patients who have COVID-19 or are at high risk of being COVID-19 positive into DISCUS (including the mechanistic study) depends on the clinical condition of the patient and lies with the local investigators.

DISCUS does not require participants to attend scheduled visits to the hospital and, therefore, there is no risk of COVID-19 transmission resulting from such visits. All patients attending a hospital site for follow-up will be expected to abide by the NHS Trust and University policies on COVID-19 which include wearing suitable personal protective equipment (PPE) provided by the NHS Trust on arrival, adhering to the visitor policy on social distancing and following one-way routing systems whilst on site.

TSCI patients will be at the MTC initially and in spinal injuries units subsequently for rehabilitation regardless of whether they participate in DISCUS or not. Therefore, participating in DISCUS does not increase the risk of patient exposure to COVID-19.

13.2 Research-Specific Visits

We will try to align the schedule of study assessments with the routine clinical pathway. . The additional risk of exposure to COVID-19 has been assessed by the Chief Investigator and Research Team as well as the relevant Trust Clinical Care Group Lead and deemed acceptable.
Patients will be made explicitly aware of the additional risk of a research-specific visit on site, that they are under no obligation to participate in the research without prejudice to their routine care and will be checked for symptoms by the research team prior to attending the site and again on the day of the visit.
This information is clearly outlined in the Patient Information Sheet and provides contact details for the research team who can direct patients to the relevant clinical service if they believe they have developed symptoms of COVID-19 or have any concerns or queries.

13.3 Protocol aligned with routine care / remote activities

The schedule of study assessments has been designed so that they align with the current routine clinical pathway for this patient population.
[OPTIONAL] The schedule of study assessment has been designed to allow for remote [recruitment, consent, follow-up etc.] which is thought to minimise the additional risk of exposure to COVID-19 to both research participants and staff through participation in this research.
Therefore, research participants and site staff are not perceived to be at any additional risk of exposure to COVID-19 through participation in this research study.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a REC for the trial protocol, patient facing information and informed consent forms. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial. Amendments may also need to be reviewed and accepted by NHS R&D departments before they can be implemented in practice at sites. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the trial. If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

14.2 Peer review

The trial including the protocol was reviewed by:

1) The NIHR/EME (funder)
2) The Society of British Neurological Surgeons' Academic Committee

This study has been/will be adopted by the NIHR CRN. In doing so the study has undergone high quality peer review by the NIHR/EME which is:

1) INDEPENDENT: Seven individual experts have reviewed the trial. The definition of independent used here is that the reviewers were external to the investigators' host institution and not involved in the trial in any way. Reviewers were anonymous.

2) EXPERT: Reviewers had knowledge of the relevant discipline to consider the clinical and/or service-based aspects of the protocol, and/or had the expertise to assess the methodological and statistical aspects of the trial.

3) PROPORTIONATE: Peer review was by seven experts, commensurate with the size and complexity of the trial. DISCUS is a large, multicentre study that had a higher level (more reviewers with broader expertise as well as the NIHR/EME independent review committee and finance committee), and potentially international peer review.

14.3 Public and Patient Involvement

In consultation meetings with TSCI patients organised by Dr Saadoun (on the 9th September 2018 with patients and families, and the 13th May 2019 with Spinal Injuries Association (SIA) members), the consensus was that this is a worthwhile trial that could improve outcome after TSCI. We discussed study design, consenting process and outcome measures. Based on these meetings, we increased the time window for patients to decide on participation, included functional, bladder and bowel outcomes and agreed to disseminate the study findings via the SIA. Another issue raised by the patients, which will be part of the initial site visit, is how to present information to potential patients and families and how it is important to also explain the potential risks associated with the duroplasty so as to balance the argument for and against the participation in the RCT. Patients will be provided with a PIS for the main trial that also includes information about mechanistic studies.

One of our co-applicants (S. Dowd) is a TSCI patient who previously had ISP and MD monitoring. He regularly appears on TV, radio, newspapers and online describing his experiences and will help promote the study within the TSCI patient community and the general public as well as disseminate the findings. Mr. Dowd has reviewed the protocol and will be consulted on future amendments.

We further discussed the study with patients who have had ISP monitoring at St. George's (on 3rd December 2019) and asked them whether they think that the proposed setup for randomisation, including the family providing consent in place of the patient, is acceptable. We also discussed whether 2 hours minimum between providing patient/family information on paper and in discussion and obtaining consent is adequate. The responses were unanimously that the current design of the study in terms of consent and randomisation is acceptable to them.

A number of patients also expressed a desire for involvement in the writing of the patient information sheet, and relevant details for inclusion on the trial website.

Further details are provided in the PPI section in the application form online.

Travel expenses for attendance at meetings will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

14.4 Regulatory Compliance

The trial will not commence until Favourable REC opinion has been obtained. The trial does not use ionising radiation other than X-Rays and CT scans done as part of standard clinical care before the patient has been recruited into the DISCUS trial. The trial does not use radioactivity.

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. Different arrangements for NHS and non NHS sites are described as relevant.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

14.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. Any Protocol deviations must be reported immediately to SITU without delay. If the deviation is classified as a serious breach, SITU will report to the sponsor.

14.6 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree:

1) The safety or physical or mental integrity of the participants of the trial; or
2) The scientific value of the trial

SITU will be notified immediately of any case where the above definition applies during the trial conduct phase. SITU will notify the licensing authority and sponsor in writing of any serious breach of:

1) The conditions and principles of GCP in connection with that trial; or
2) The protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

14.7 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles.

The study staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database. Consent will be obtained to store participant identifiable data at the central study office in Oxford. This is required to facilitate the follow up regime. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Further information detailed in section 11.0

14.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

At the time of writing the protocol, we are unaware of any competing interests that might influence trial design, conduct, or reporting of the DISCUS trial. There are no ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. There are no commercial ties requiring disclosure that include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company. There are no non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

At the time of writing this protocol not all sites/personnel have been identified. If any such competing interests arise, this section of the protocol will be modified accordingly.

14.9 Indemnity

City St George's University of London (the Sponsor) holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that City St George's has been negligent. This includes negligence in the writing of the protocol, or selection of trial resources. Where the Trial is conducted in a hospital, the hospital has a duty of care to participants. City St George's University of London will not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. If a participant indicates that they wish to make a claim for compensation, this needs to be brought to the attention of City St George's University of London immediately. Failure to alert City St George's University of London without delay and to comply with requests for information by the sponsor or any designated Agents may lead to a lack of insurance cover for the incident.

14.10 Amendments

The sponsor may make a non-substantial amendment at any time during the trial. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amendments also need to be notified to the HRA and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the HRA and REC. The only circumstance in which an amendment may be initiated prior to HRA and REC approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the HRA and REC approval has been obtained.

14.11 Access to the final trial dataset

The Chief Investigators, Professor Marios C. Papadopoulos and Dr Samira Saadoun, will be the custodians of the data.

DISCUS trial data will be accessible to Sponsor representatives, representatives of the Surgical Intervention Trials Unit and the Oxford Clinical Trials Research Unit at the University of Oxford; and responsible individuals identified by the Sponsor, including representatives of Regulatory authorities and NHS trust.

During the trial, access to the trial data will be limited to the monitoring and data cleaning activities required to deliver the trial objectives and for the purposes of regulatory and safety reviews.

DISCUS trial data will be stored on the trial database and any paper documents will be stored in a locked filing cabinet at the trial office. The final dataset will be archived electronically on a University of Oxford Server. At the end of the trial, all paper documents will be archived as outlined section 11.4. Participating sites will store their site and patient files in accordance with the requirements stipulated by their local R&D governance policies.

All participating patients and their families/carers will be asked at the time of recruitment if they would like to receive a copy of the trial results. This will be written collaboratively with clinicians and patient representatives and distributed accordingly.

Engagement will be maintained with the SIA. The wider public will be alerted via links with relevant organisations / charities, and the Research Media Offices. Engagement with the NIHR Dissemination Centre will also be sought, to ensure global awareness of study findings. City St. George's University London and St. George's NHS Trust have professional communication officers. It is anticipated that together these individuals, and NIHR equivalents, will agree an effective communication strategies including co-ordinated press releases, interviews etc.

OCTRU maintains a list of all ongoing and completed trials, with all publications on its website even when trial websites are archived. (https://www.ndorms.ox.ac.uk/octru/trials-portfolio/trialscompleted). Given the potential involvement of up to 26 MTCs in the UK, and the positions held by co-applicants and collaborators within the national and international neurosurgery community, the results will rapidly reach the neurosurgery Multi-Disciplinary Teams, ensuring the trial findings improve practice and service delivery for TSCI patients within the NHS.

15. DISSEMINATION POLICY

Publication is defined as "Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated.

The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives. To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

BEFORE THE OFFICIAL COMPLETION OF THE TRIAL: All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the Steering Committee/the Funder shall have the final say. Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

UP TO 180 DAYS AFTER THE OFFICIAL COMPLETION OF THE TRIAL: During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication. The Chief Investigator shall be senior and corresponding author of the Main Publication. Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order. Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration. Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well. If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

BEYOND 180 DAYS AFTER THE OFFICIAL COMPLETION OF THE TRIAL: After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60)

days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

Archiving Arrangements

Each site will be responsible for their onsite level study archiving. The trial essential TMF along with any central trial database will be archived in accordance with the sponsor SOP.

See also Section 11.4

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17. APPENDICIES

17.1 Appendix 1 - Risk

Risks associated with trial interventions
☐ A ≡ Comparable to the risk of standard medical care
☒ B ≡ Somewhat higher than the risk of standard medical care
☐ C ≡ Markedly higher than the risk of standard medical care

JUSTIFICATION: The RCT involves performing a duroplasty that carries a small risk as detailed below. Insertion of the pressure and MD probes intradurally also carries a small risk. Therefore, the study is classed at B.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
Intervention	Body system/Hazard	Activity	Frequency	Comments
Duroplasty	1. CSF leak 2. Wound infection 3. Meningitis (septic) 4. Pseudomeningocele	1. Wound re-suture / lumbar drain 2. Ioban, Antibiotics 3. Antibiotics 4. No treatment, spontaneously resolves	1. Once / 5 days 2. 1-2 weeks 3. 1-2 weeks 4. N/A	1-3) Reducing CSF leak also reduces risk of wound infection and meningitis. Use of nylon sutures for skin closure, which are more watertight than staples. Apply a waterproof film dressing (e.g. Ioban®, which is a betadine impregnated adhesive dressing) over the wound for one week. Placing the wound drain on gravity (rather than suction) for a week. Sit up patient to >45^0 for a week to reduce cervical CSF pressure. Remove the sutures at two weeks. Suture dural patch to dural edges, rather than merely apply the duroplasty without suturing it. Sutures to tighten skin around probes to reduce CSF leak. 4) Pseudomeningocele spontaneously resolves 6-7) The probes are inserted under microscope and advanced parallel to the cord
ISP / MD monitoring	1. CSF leak 2. Wound infection 3. Meningitis (septic) 4. Pseudomeningocele 5. Probe displacement 6. Neurological deterioration 7. Haematoma	1. Wound re-suture / lumbar drain 2. Ioban, Antibiotics 3. Antibiotics 4. No treatment, spontaneously resolves 5. Disconnect when moving patient 6. Insert probe under microscope 7. Insert probe under microscope, Haemostasis	1. Once / 5 days 2. 1-2 weeks 3. 1-2 weeks 4. N/A 5. Each time 6. Once 7. Before closure	

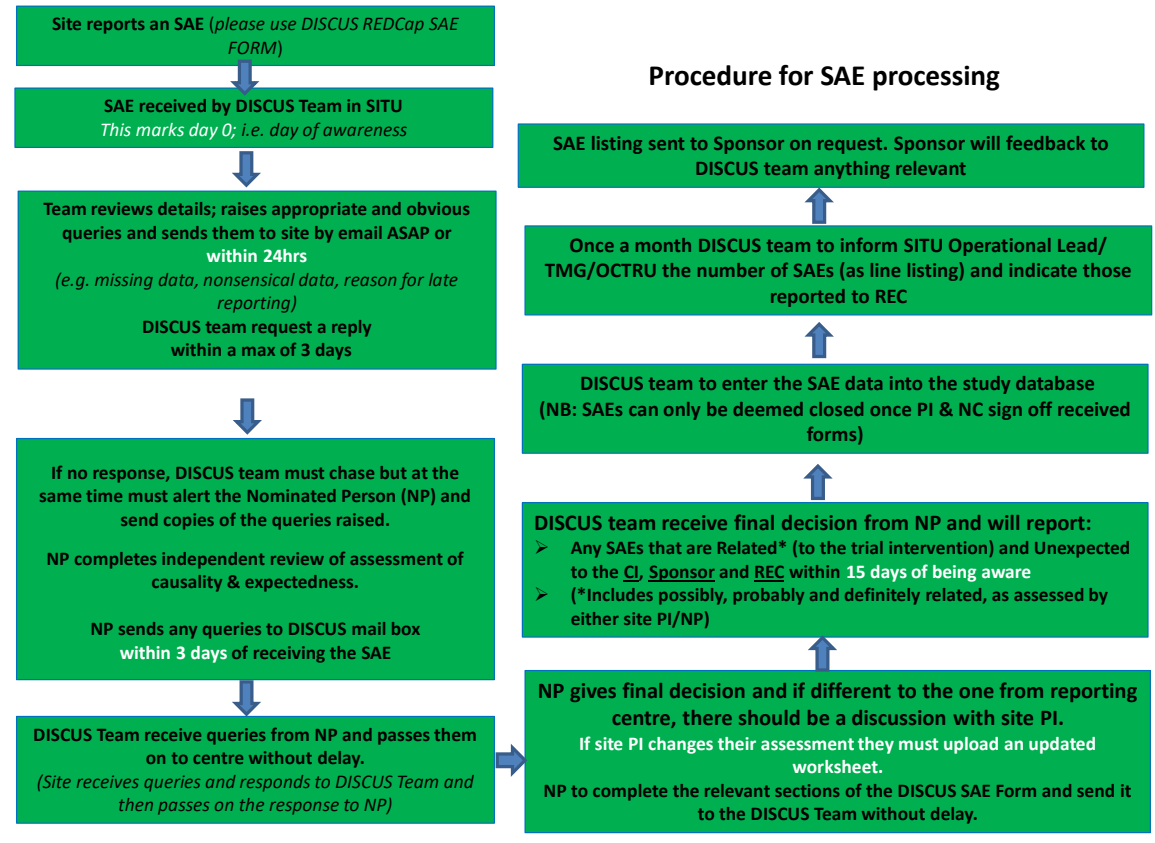
Should surgical complications / adverse events above that typically expected be reported, these will be reviewed by the Data Safety and Monitoring Committee (DSMC).

17.2 Appendix 2 - Schedule of Procedures

PROCEDURE	Admission	Treatment	Monitoring (optional)					End of study
	Day 1	Days 1-3	Days 1-5	Days 14+/-7	Months 1-3	Month 3	Month 6	Month 12
ISCSCI assessment	x						x	
CT spine	*x							
MRI spine	x			x				
Eligibility assessment	x							
Informed consent	x							
Randomisation	x							
CRF part I	x							
Surgery		x						
Pressure monitoring			(x)					
MD monitoring			(x)					
Transfer from MTC to Spinal Injuries Unit					x			
HRQoL (SF-36, SCI-QL23)							x	x
SCIM III, WISCI II, CUE-Q, grip strength							x	
Record of complications				x		x	x	x

*only if done as part of standard of care

17.3 Appendix 3 - Safety Reporting Flow Chart



DISCUS_SAEProcessingFlowchart_V0.1_28Sep2020

17.4 Appendix 4 - Amendment History

Amendment History				
Amendment No.	**Protocol version no.**	**Date issued**	**Author(s) of changes**	**Details of changes made**
N/A	V1.0 to V2.0	24May2021	PS/DISCUS team	V2.0 was first accepted version of the protocol by REC
AMD02_NSA002	V3.0	09Dec2021	PS/DISCUS team	Minor clarifications after data base design
AMD04_SA001	V5.0	08Mar2022	PS/DISCUS team	Addition of emergency consent/ procedures resulted in V4.0_04Feb2022, and with *or consultee advice* addition was updated to to V5.0_08Mar2022
AMD07_NSA006	V6.0	30May2022	Jo Cook (Interim Trial Manager)/DISCUS Team	Clarification of the imaging procedures (MRI/CT scans) mentioned throughout the protocol.
AMD11_SA002	V8.0	17Jul2023	Melody Chin/DISCUS Team	Removal of SF-36 at 3 months and update trial manager and lead statistician details
AMD14_SA003	V9.0	24Jan2025	Melody Chin/DISCUS Team	Updated St George's to City St George's following the merger of City and St George's, University of London on 01st August 2024. Updated DSMC member to Mr Sorin Bucur. Removal of QRI representative from TMG and TSC.
AMD16_NSA013	V10.0	05Dec2025	Sophie Reynolds/DISCUS Team	24 month recruitment extension. Update of trial manager details. Update for clarity of appendix 3. Update to confirm non-UK sites recruit to study. Minor formatting changes.

List details of all protocol amendments here whenever a new version of the protocol is produced. Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.