

**STUDY PROTOCOL**

**UNDERSTANDING CAUDA EQUINA SYNDROME  
(UCES)**

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STUDY PROTOCOL

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## ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
BASS	British Association of Spine Surgeons
BNTRC	British Neurosurgical Trainee Research Collaborative
BOTA	British Orthopaedic Trainees Association
CES	Cauda Equina Syndrome
CESI	Cauda equina syndrome - incomplete
CESR	Cauda equina syndrome - retention
CESS	Cauda equina syndrome - suspected
CHI	Community Health Index
CI	Chief Investigator
CRF	Case Report Form
DGH	District General Hospital
DRE	Digital Rectal Examination
EU	European Union
GCP	Good Clinical Practice
ICMJE	International Committee of Medical Journals Editors
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10 <sup>th</sup> version
ICH	International Conference on Harmonisation
ISF	Investigator Site File
MRI	Magnetic Resonance Imaging
NHS	National Health Service
PACS	Picture Archiving and Communications System
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SOP	Standard Operating Procedure
UCES	Understanding Cauda Equina Syndrome
UK	United Kingdom

## SUMMARY

Cauda equina syndrome is a potentially devastating condition caused by compression of the cauda equina nerve roots. This can result in bowel, bladder and sexual dysfunction plus lower limb weakness, numbness, and pain. Cauda equina syndrome occurs infrequently but has serious potential morbidity and medico-legal consequences. This study aims to identify and describe the presentation and management of patients with cauda equina syndrome in the United Kingdom using trainee research collaborative networks. This will provide accurate incidence figures, establish current clinical practice, allow assessment of the adherence to national published standards of care, and determine patient outcomes from this condition. Accurate, up to date information about the presentation, management, and outcome of patients with cauda equina syndrome will inform standards of service design and delivery for this important but infrequent condition and help to identify future research priorities.

# 1 INTRODUCTION

## 1.1 BACKGROUND

Cauda equina syndrome (CES) is a rare but potentially devastating condition caused by compression of the cauda equina nerve roots. This most commonly occurs due to a prolapsed intervertebral disc. The clinical syndrome includes any of bilateral sciatica, saddle anaesthesia, bladder, bowel, and sexual dysfunction.<sup>1-3</sup> The disabling nature of these symptoms causes significant medical and social morbidity and high health and social care costs. In addition, litigation related to the management of CES leads to significant medicolegal workload and costs.<sup>1,4,5</sup>

Due to the consequences of CES for patients and society, several groups have issued clinical guidance or standards of care for CES.<sup>1,6-8</sup> However, the evidence base for current clinical guidance consists of small retrospective single centre case series.<sup>1,9,10</sup> Even systematic reviews of outcomes in CES have included relatively few patients, with the largest including 464 patients.<sup>9,11</sup> Lack of a clear definition of CES has hampered comparative analysis of historic studies, and different interpretations of the available evidence have been offered.<sup>10,12</sup> A diagnosis of CES encompasses patients presenting with any of urinary hesitancy, complete painless urinary retention, perineal or perianal numbness, faecal incontinence, sexual function disturbance, or bilateral sciatica, but patients may also experience lower limb weakness, numbness, or unilateral sciatica.<sup>2,3,13</sup> Accurate division of CES into subtypes of suspected (CESS), incomplete (CESI), and with retention (CESR) can help to clarify understanding of outcome studies and develop care standards appropriate to the presentation,<sup>1,14</sup> but the current evidence is based on a small number of patients.

Retrospective case series in the UK have identified approximately 15-31 patients per year per specialist neurosurgical or spinal centre with confirmed CES.<sup>3,13,15,16</sup> Estimates of the incidence of CES range from 1-7 per 100,000 population.<sup>17,18</sup> In 2010-2011 in England, 981 surgical decompressions were performed for CES according to hospital episode statistics,<sup>19</sup> and the population was estimated at 52,234,000,<sup>20</sup> giving an incidence of 1.9 per 100,000 for operated CES. Although CES is not common, there may still be over 1000 patients managed for CES in the UK per year. Accurate data on the presentation and management of these patients would establish current management and adherence to and feasibility of care quality statements as well as potentially informing the revision of guidance based on accurate and current data.

The British Neurosurgical Trainee Research Collaborative (BNTRC) has previously successfully used a network of neurosurgical trainees across the United Kingdom (UK) and Ireland to identify cases via local tertiary referral systems in conditions such as chronic subdural haematoma.<sup>21</sup> As CES is managed in the UK and Ireland by specialist spinal services, similar case ascertainment via specialist referral systems to neurosurgical, orthopaedic, or joint spinal services provides a method of accurately identifying patients with CES during hospital admission. This would allow prospective identification and assessment of large numbers of patients across the UK and Ireland over a defined time period, and lead to the largest prospective observational cohort study of CES.

We propose to carry out the first national cohort study of the presentation and management of CES in the UK and Ireland and establish the largest prospective series of patients with CES. This will provide data on CES incidence, epidemiology, presentation, management, and outcomes. This will inform the development of clinical guidance and identify areas for future research in this condition.

## 1.2 CURRENT STANDARDS OF CARE

The British Association of Spine Surgeons (BASS) standards of care for suspected and confirmed compressive CES issued in 2015 include the following main statements.<sup>6</sup>

- Imaging, usually Magnetic Resonance Imaging (MRI), should be undertaken as an emergency.
- Decompressive surgery should be undertaken at the earliest opportunity, taking into consideration the duration of pre-existing symptoms and the potential for increased morbidity while operating in the small hours.
- Patients should be counselled that the aim of surgery is to preserve that function present at the time of surgery.

The Society of British Neurological Surgeons Care Quality Statement issued in October 2015 includes the following statements relevant to the management of patients with CES.<sup>8</sup>

- Appropriate and timely management of acute neurosurgical disorders should always take priority over less urgent elective cases.
- All patients should be appropriately investigated in a timely manner by secondary care prior to referral.
- It is not appropriate that neurosurgical staffs are called upon to act as a scanning service and a diagnosis should be reached prior to referral.
- Out of hours MRI scanning for emergency or urgent clinical problems should be considered to be routine practice prior to referral in order to prevent the needless and potentially harmful transport of patients for diagnostic imaging.
- Trusts must make remote access to imaging instantly available to Consultant Neurosurgeons and Neuroradiologists.

A proposal for evidence based guidance for the management of CES in the UK included the following suggestions.<sup>1</sup>

- Accurate history taking of relevant symptoms should be undertaken, including bilateral radicular pain, dermatomal sensory loss, myotomal weakness, and any change in bladder or bowel function.
- Careful examination should be performed to identify objective signs of bilateral radiculopathy, including reflex changes, dermatomal sensory loss, and myotomal weakness.
- Examination of the perineum and digital rectal examination (DRE) should be performed.
- Ideally the MRI should be performed at the District General Hospital within one hour of the request.
- Patients with CESI or CESR with uncertain, early, or preserved cauda equina function should have MRI and surgery as an emergency by day or night
- Patients with CESS can have MRI imaging the following morning with consideration of operating on the same day.
- Patients with prolonged CESR, who are uncertain CES, or who have no preservation of cauda equina function clinically can be operated on the following morning acute list.
- Surgery should be carried out by a consultant spinal surgeon or as a minimum a trainee directly supervised by a consultant

## 2 OBJECTIVES

This prospective observational cohort study aims to:

- Identify the number of cases of CES in the UK in all collaborating centres
- Describe the presenting symptoms and signs in patients with CES
- Describe the pathways of presentation to specialist spinal services for patients with CES in the UK and Ireland
- Describe the type and timing of investigation of patients with CES
- Describe the medical and surgical management of CES
- Compare current practice to standards of care for CES
- Describe clinical outcomes for patients with CES using validated patient reported outcome measures, stratified by presentation, investigations, and management
- Demonstrate the ability of neurosurgical and orthopaedic surgical trainee networks to collaborate successfully on a prospective cohort study

## 3 STUDY DESIGN

Understanding Cauda Equina Syndrome (UCES) is a prospective cohort study of patients with confirmed CES managed at specialist spinal centres in the UK.

Cases will be identified by neurosurgical or orthopaedic trainees in each specialist centre through daily screening of tertiary referrals and admissions to specialist spinal services. All patients managed as CES by the treating team will be included in this audit. CES will be divided into CES suspected (CESS), CES incomplete (CESI), and CES retention (CESR).



Data regarding timing and type of symptom onset, referral, investigation, management, and outcome will be recorded anonymously on a secure database by the local trainee investigator during the patient's hospital admission and after discharge. Patient consent will be sought for the use of their data and patients will be asked to complete patient reported outcome measures representing their condition before surgery and up to one year after surgery. Their MRI scans at presentation will also be collected. This data will be compared with care quality statements and published outcome data for CES.

The study will recruit for one year. Cases will be identified from admissions to spinal units between 1<sup>st</sup> June 2018 until 31<sup>st</sup> May 2019. The last one year follow up assessments will be sent to participants on 1<sup>st</sup> June 2020.

This is an observational study. No changes to routine patient care will occur during this study.

## **4 STUDY POPULATION**

### **4.1 NUMBER OF PARTICIPANTS**

This study aims to establish a case series of patients with CES. We expect approximately 20 patients per spinal centre per year depending on the population served, and a total of approximately 600-1000 patients in one year across the UK.

### **4.2 INCLUSION CRITERIA**

For inclusion in this study, the patient must:

- be over 18 years old;
- be admitted to a specialist spinal service in the UK between 1<sup>st</sup> June 2018 and 31<sup>st</sup> May 2019;
- have capacity to provide informed consent for participation in this study; and
- have a diagnosis of clinical CES and structural compression of the cauda equina on imaging as determined by the treating clinician.
  - Clinical CES includes any of: altered saddle sensation; bladder dysfunction; bowel dysfunction; sexual dysfunction; or bilateral sciatica. This should be associated with radiological compression of the cauda equina. The cauda equina compression can be due to any cause, including, but not limited to, disc, tumour, infection, etc.

There is no upper age limit as we aim to establish the demographics of those presenting with CES. Participating centres are listed at the beginning of this protocol.

### **4.3 EXCLUSION CRITERIA**

- Patients under 18 years old
- Patients undergoing emergent decompression for unilateral motor or sensory symptoms (eg foot drop), without clinical evidence of CES
- Patients referred with suspected CES where the diagnosis is not confirmed, for example:
  - Patients with the clinical symptoms and signs of CES without radiological evidence of cauda equina compression
- Patients not admitted to participating spinal centres in the UK
- Patients admitted to a participating spinal centre before 1<sup>st</sup> June 2018 or after 31<sup>st</sup> May 2019
- Patients who are unable to provide informed consent for participation in this study

### **4.4 CO-ENROLMENT**

Co-enrolment in any other ongoing studies will be allowed.

## **5 PARTICIPANT SELECTION AND ENROLMENT**

### **5.1 IDENTIFYING PARTICIPANTS**

All neurosurgical and orthopaedic units managing patients with CES in the UK will be invited to participate. All patients admitted with radiologically confirmed CES will be identified by the lead local investigator via the screening of referral and admission systems at their spinal unit. All lead local investigators must be members of the clinical team caring for patients with CES in their unit.

Capture-recapture methods will be used to ensure complete case ascertainment. In December 2018, June 2019, and December 2019 all local investigators will check their case ascertainment by asking their local coding departments for all discharges coded as CES using the diagnostic code ICD-10 G83.4. Any additional patients identified through this method that meet the inclusion criteria will be contacted by a member of the clinical team caring for the patient and invited to participate.

### **5.2 CONSENTING PARTICIPANTS**

Once patients have been identified as being eligible to participate in the study, they will be asked by a member of their clinical team whether they would be willing to receive further information about the study. For the majority of patients this will occur during their admission to the spinal unit, and the approach will be made by a member of ward medical or nursing staff. Once verbal consent has been gained to give further information about the study, patients will be provided with the information leaflet for the study. Patients who indicate that they are happy to have further discussions regarding the study will be visited in hospital by a member of their clinical team to complete the written consent process. The person undertaking written consent will be adequately trained to do so, and have a good knowledge of the study protocol, aims, and processes.

Decompression surgery for CES takes place as an emergency, and admissions occur at all times of day and night throughout the week and weekend. Following decompressive surgery the length of stay in hospital wards may be as short as one to two days, or may be longer than a week when there are ongoing bladder or bowel problems. All patients will be given adequate time to read the information leaflet with a minimum time period of six hours. Some patients will be discharged prior to being identified as being eligible for the study. These patients will be contacted by telephone by a member of the clinical team and asked if they would be willing to receive information about the study by post or email. If they agree, the information leaflet and consent form will be sent to them, and they will be re-contacted to go through the consent process over the telephone at least 24 hours after receiving the information.

All patients who are eligible for inclusion in the study will have basic anonymous clinical data collected as part of the screening log to establish participation rates and incidence at each centre. This will allow accurate assessment of the incidence of CES. Patients who do not wish to participate in the study will not be contacted further for the completion of patient reported outcome measures.

### **5.3 WITHDRAWAL OF STUDY PARTICIPANTS**

Participants are free to withdraw from the study at any point. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's electronic case report form. The participant will not be contacted any further for outcome measures but their basic anonymous clinical details will be retained to allow accurate epidemiological assessment of the incidence of CES. If a patient loses capacity to consent for ongoing participation during the course of the study, the data they have already submitted or has already been submitted by their clinical team with their consent will continue to be used in the study, but they will not be contacted with further questionnaires.

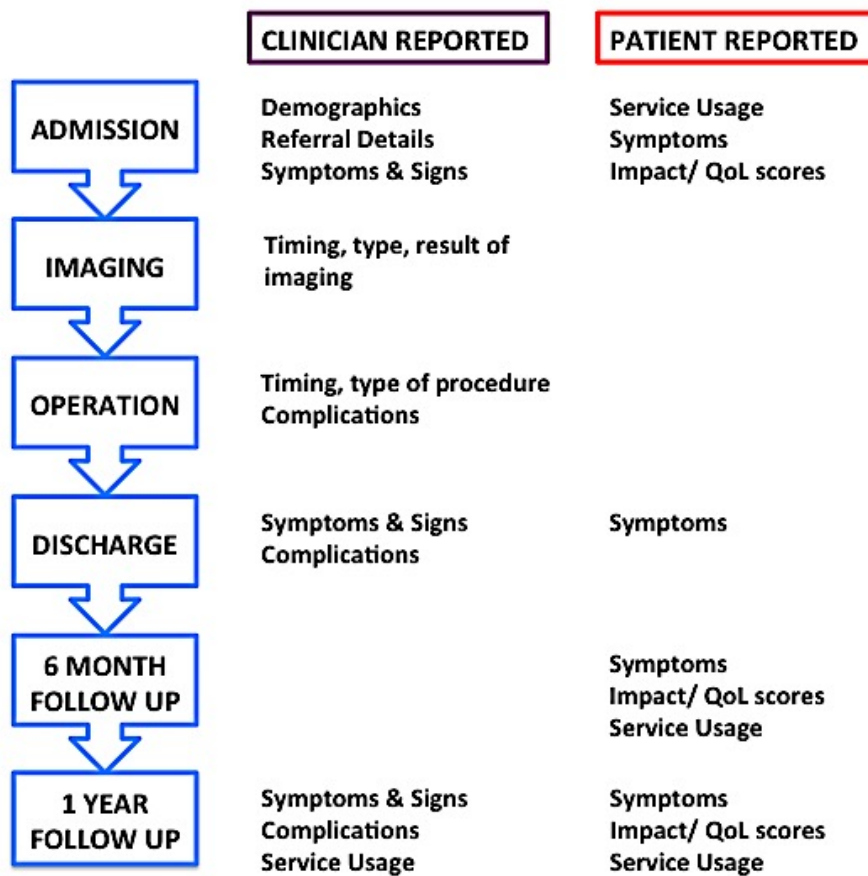
## **6 DATA COLLECTION**

Data relating to presentation, hospital admission, investigations, and follow up will be collected by the local trainee investigator who is a member of the clinical team caring for the patient. Data will be collected from the patient's notes, through routine interaction with the patient as part of clinical care, and through interaction with other staff members caring for the patient. All clinical and demographic information collected for this study by the local investigators is collected routinely for clinical care. No extra assessments will be performed.

Study participants who have consented to participate will also be asked to fill out details about their patient journey to the spinal unit, their symptoms, patient reported outcome measures, and service usage. These will be collected electronically anonymously via the electronic database and linked to the patient record. Patient reported outcome measures will include visual analogue scores for back and leg pain, the Oswestry Disability Index,<sup>22</sup> the neurogenic bowel dysfunction score,<sup>23</sup> the short form incontinence questionnaire,<sup>24</sup> and the Arizona sexual experiences scale.<sup>25</sup>

The timing and type of clinical reported and patient reported data that will be collected is shown in Figure 1: Study Flow Diagram.

**Figure 1: Study Flow Diagram.** Time points and types of data collection in UCES.



Data will be entered anonymously into a study specific secure database hosted by Castor EDC. Castor EDC complies with all applicable laws and regulations: Good Clinical Practice (GCP), European Union(EU) Annex 11, and the European Data Protection Directive. Clinician entered data will be entered directly into the database using the participant's unique study number. This study number is assigned on creating a new patient record in the database. The clinical team can only view the records of patients from their own centre. Once a participant consents for their email address to be held securely in the database, participant questionnaires are sent out via email. Each email contains a unique link for that participant with the questionnaires to complete. The responses are linked by the database to the patient's record. The participant's email address is entered by the local clinical team and this field is stored securely and is encrypted and cannot be viewed by anyone outside of the patient's local centre.

Some patients may not have an email address or may prefer to fill out questionnaires on paper. In these cases, paper questionnaires for admission and discharge time points will be provided by the local team and returned to the central study team by post identified only using the patient's unique study number.

Where patient data is routinely entered into spinal databases, surgical and outcome data from those databases will be linked anonymously to the patient record by the clinical team who routinely enter that data using the patient's unique identifier for that database or registry.

Imaging at presentation will also be reviewed on local PACS systems. We will ask for patient consent for review of imaging by the study team. All identifiable images will be stored and transferred within the NHS PACS network. Only anonymised scans will be processed outside the NHS PACS network. Anonymised imaging data will be labelled only with the study number and stored on anonymised CDs or on encrypted hard drives and processed using computers with limited access via usernames and passwords.

All local investigators will store a copy of the link between the patient's unique study number and their contact details, National Health Service (NHS) number, hospital number, Community Health Index (CHI) number, unique identifiers for spinal databases or registries, or other identifying details on a secure password protected NHS computer. Consent forms will be stored securely in a locked NHS office. No identifying information will be entered into the secure database except the email address.

When participants prefer to fill out paper questionnaires or do not respond to the email link, their contact details (name, address, telephone number) will be passed to the central study team at NHS Lothian using the NHS email system with the consent of the patient. The central study team will contact the participants to find out whether they still wish to take part in the study. Those who wish to continue with the study will be sent the questionnaires by email, by post, or they can be completed over the telephone with a member of the central study team depending on the preference of the participant. If participants do not wish to continue with the study, they will not be contacted further.

## **7 STATISTICS AND DATA ANALYSIS**

### **7.1 SAMPLE SIZE CALCULATION**

We plan to establish the number of patients presenting with CES in the UK over one year. We expect to identify between 600-1000 patients with CES. Our identification and recruitment rates will be checked using capture-recapture techniques using hospital discharge diagnosis coding and existing spinal registries. Previous BNTRC projects have included all UK neurosurgical units.<sup>21</sup>

### **7.2 PROPOSED ANALYSES**

#### **7.2.1 INCIDENCE OF CES**

The incidence of CES will be established based on the number of patients identified at each unit and the catchment population of that unit. If all units in the UK participate, incidence will be calculated based on UK population estimates. The incidence figure will be based on all patients identified as being eligible for the study, even if they do not consent for further participation.

#### **7.2.2 CHARACTERISTICS OF PATIENTS WITH CES**

A descriptive analysis of the clinical and demographic characteristics of presenting symptoms, signs, and outcomes of patients with CES will be performed. This will be determined from both clinician reported and patient reported data. CES incidence and characteristics will be broken down into the categories of CESS, CESI, and CESR based on the clinical data. The categorical and quantitative findings on imaging will also be described.

#### **7.2.3 METHODS OF PRESENTATION TO SPECIALIST SERVICES**

Methods of patient presentation to specialist services will be described. Type, timings, and findings of investigations in patients presenting via different routes will be compared.

#### **7.2.4 ASSESSMENT OF ADHERENCE TO QUALITY STANDARDS**

The investigation and management of patients with CES will be described and compared to that laid out in the care quality standards presented in section 1.2. Proportions meeting the standards will be reported.

### **7.2.5 CES OUTCOMES**

Patient outcomes will be assessed and analysed using both clinician and patient reported outcome measures at six months and one year. Patient outcomes will be stratified by demographics, presenting features, timing and findings of investigations, and timing and type of surgery.

### **7.2.6 SERVICE USAGE**

Patient usage of healthcare services over the year following diagnosis and management of CES will be assessed using both patient reported service usage and electronic records.

## **8 OVERSIGHT ARRANGEMENTS**

### **8.1 INSPECTION OF RECORDS**

Investigators and institutions involved in the study will permit study related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection if required. In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation. A study specific risk assessment may be performed by representatives of the sponsor if required. The outcomes of the risk assessment will form the basis of any monitoring or audit plans.

## **9 GOOD CLINICAL PRACTICE**

### **9.1 ETHICAL CONDUCT**

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

### **9.2 INVESTIGATOR RESPONSIBILITIES**

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

#### **9.2.1 INFORMED CONSENT**

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved. Participants must receive adequate oral and written information – appropriate Participant Information Leaflets and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Leaflet and Consent Form. The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled. The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor. The Investigator or delegated member of the study team and the participant will sign and date the informed consent form to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF).

#### **9.2.2 STUDY SITE STAFF**

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

### **9.2.3 DATA RECORDING**

The Principal Investigator is responsible for the quality of the data recorded in the database at each site.

### **9.2.4 GCP TRAINING**

All researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement. GCP training status for all investigators should be indicated in their respective CVs.

### **9.2.5 CONFIDENTIALITY**

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

### **9.2.6 DATA PROTECTION**

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor and representatives of regulatory authorities. Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

## **10 STUDY CONDUCT RESPONSIBILITIES**

### **10.1 PROTOCOL AMENDMENTS**

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

### **10.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE**

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsor and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate. Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to [QA@accord.scot](mailto:QA@accord.scot). Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

### **10.3 SERIOUS BREACH REQUIREMENTS**

A serious breach is a breach which is likely to affect to a significant degree:  
(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

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

#### **10.4 STUDY RECORD RETENTION**

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

#### **10.5 END OF STUDY**

The end of the study is 18 months after the enrolment of the last participant. The Investigators or the sponsor have the right at any time to terminate the study for clinical or administrative reasons. The end of the study will be reported to the REC, and R&D Offices and sponsor within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure. End of study notification will be reported to the sponsor via email to [resgov@accord.scot](mailto:resgov@accord.scot). A summary report of the study will be provided to the REC within 1 year of the end of the study.

#### **10.6 INSURANCE AND INDEMNITY**

The sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff. The following arrangements are in place to fulfil the sponsor's responsibilities:

- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The sponsor requires individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

## **11 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**

### **11.1 AUTHORSHIP POLICY**

Ownership of the complete dataset arising from this study resides with the steering committee and the BNTRC. On completion of the study, the data will be analysed and tabulated, and a report will be prepared. Local data collected as part of this study belongs to the local team collecting that data.

### **11.2 PUBLICATION**

The study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to investigators. Following the initial analysis and publication, study data will be made available to those who submit successful peer-reviewed proposals for use of the data to the steering committee via the BNTRC.

All local investigators who enter data for at least one case will be named as contributors on all publications arising from this study and will receive a certificate of collaboration in this study. Authorship of publications arising from this study will be determined in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE).<sup>26</sup>

### **11.3 PEER REVIEW**

The concept for this study was selected by a panel of judges in an open competition for support from the BNTRC. The protocol has been approved by the steering committee listed at the beginning of this protocol prior to the start of data collection.

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