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## Protocol For Predicting Cognitive Outcomes After Spinal Surgery

Keenan

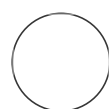
Smith<sup>1</sup>,Christopher Hawthorne<sup>2</sup>, Matthew Sheridan<sup>2</sup>,

Malcolm

Shona

Eric Jackson<sup>2</sup>, Watson<sup>2</sup>,Martin Shaw<sup>3</sup>, McKay<sup>2</sup>,Jonathan Cavanagh<sup>1</sup><sup>1</sup>University of Glasgow; <sup>2</sup>Queen Elizabeth University Hospital, Glasgow;<sup>3</sup>NHS Greater Glasgow and ClydeOPEN  ACCESS

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Keenan Smith

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We use this protocol and it's working

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**Keywords:** Delirium, Postoperative Delirium, Postoperative Cognitive Dysfunction, Perioperative Neurocognitive Disorders, Processed EEG, BIS, Bispectral Index, Neuroinflammation, CRP, Interleukin 6, IL-6, Interleukin 1-beta, IL-1B, Inflammation, Biomarkers, Spinal Surgery, Postoperative Cognitive Decline

## ABSTRACT

**Background:** Perioperative Neurocognitive Disorders range from short term (postoperative delirium) through medium (delayed neurocognitive recovery) through to long term (mild and major postoperative neurocognitive disorders, sometimes called postoperative cognitive dysfunction) [1]. They are particularly prevalent in the older population, those with pre-existing cognitive impairments and those undergoing major or emergency surgery [2]. Multiple studies have demonstrated correlation between depth of anaesthesia measured using intra-operative processed EEG and postoperative neurocognitive outcomes [3]. Similarly, links between markers of systemic inflammation and neurocognitive outcomes have been explored using both targeted studies of candidate biomarkers and untargeted proteomics studies utilising high throughput multiplex assays [4]. As yet however, the link between systemic markers of inflammation, depth of anaesthesia and perioperative neurocognitive outcomes has not been the subject of prognostic modelling.

**Aims:** The primary aim of this study will be to use supervised machine learning to build a prognostic model for postoperative delirium based on measures of systemic inflammation and depth of anaesthesia. The secondary aim of this study is to use supervised machine learning to build a prognostic model of postoperative cognitive dysfunction based on measured of systemic inflammation and depth of anaesthesia.

**Methods:** This pragmatic, observational, pilot study will aim to recruit 50 participants aged over 65 years, undergoing non-emergency spinal surgery. Participants will undergo serum inflammatory biomarkers analysis immediately prior to, and the day following surgery and this data, together with metrics derived from intraoperative processed EEG, will be compared to delirium incidence over the first 5 postoperative days. Similarly, this data will also be used to predict cognitive decline between standardised cognitive tests completed prior to surgery, and those performed at 6 months postoperatively.

## Prior to Enrolment

### 1 Screening

Patients awaiting non-emergency spinal surgery at the Queen Elizabeth University Hospital will be identified from electronic waiting lists and screened for eligibility.

## Document



NAME

**Eligibility Criteria**

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## 2 Approaching Participants

Patients eligible for inclusion will be asked by their clinical team for permission for the study team to approach, and where granted, a patient information sheet will be sent by post or email. Patients eligible for inclusion will be included in the screening log.

## Document



NAME

**Patient Information Sheet 1.2**

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# Enrolment


## 3 Consent

Following pre-operative assessment potential participants will be approached by a member of the study team and invited to participate. Potential participants will be given the opportunity to ask any questions they have and, following confirmation of eligibility, will be invited to provide informed consent to participate.

Document	
	NAME <b>Consent Form</b>
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## 4 Study Enrolment

Following enrolment in the study participants will be allocated a participant number and a record of their enrolment in the study will be entered into their patient notes. A letter will be sent to their GP confirming their enrolment in the study and the participant will be given a copy of their consent form to take away with them.

Document	
	NAME <b>GP Letter</b>
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## Initial Assessment

### 5 Initial Assessment

Directly following enrolment, participants will undergo an initial assessment consisting of a semi-structured interview, a physical rating, cognitive testing, a mental health assessment, and a relative or friend will act as an informant for a Short IQCODE.

#### 5.1 Semi-Structured Interview

A semi-structured interview will gather information on patient demographics, past medical history, medication history, smoking status and alcohol consumption.

#### 5.2 Physical Rating

Participants will be reviewed by an anaesthetist for ASA status and will complete an Edmonton Frailty Score.

### 5.3 Cognitive Testing

Participants will undergo a Mini Mental State Exam (MMSE), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and Trail Making Tests A & B, administered by appropriately qualified assessors.

### 5.4 Mental Health Assessment

Participants will be interviewed about any personal or family history of mental illness and any medications taken for psychiatric diagnoses. They will also complete a Generalised Anxiety Disorder Assessment (GAD-7) and a Patient Health Questionnaire (PHQ-9).

### 5.5 Short IQCODE

Participants will be asked to bring an informant, in the form of a relative or friend who knows them well, with them to their initial assessment. This informant will be asked to complete a short IQCODE.

## Day of Surgery

### 6 Consent to Continue

Participants will be greeted on the day of surgery and will be asked to confirm whether they're happy to continue in the study.

Step 6 includes a Step case.

#### Cancellation

step case

#### Cancellation

In the event that the surgical procedure has to be rescheduled following enrolment in the study, the initial assessment will be considered valid for 12 weeks, after which it will be repeated if the participant is still happy to participate in the study.

### 7 Pre-Operative Blood Sampling

Participants will undergo venous cannulation prior to induction of anaesthesia for their surgery. A 4ml sample of blood will be taken from the venous cannula prior to flushing with 0.9% Sodium Chloride solution and stored in a blood sampling vial containing Ethylenediaminetetraacetic acid (EDTA). The sample will be transported to the School of Infection and Immunity at the University of Glasgow where it will be centrifuged and stored for analysis.

## 8 Intra-operative Depth of Anaesthesia Monitoring

Prior to induction of anaesthesia participants will have electrodes attached to their forehead which will be attached to a depth of anaesthesia monitor, BIS (Covidien). The monitor will record processed EEG data from prior to induction of anaesthesia through to the end of the operation. After the operation the data will be transferred to a USB drive and stored securely.

## 9 Intra-operative Anaesthetic Data

Data regarding vital signs, administered medicines and fluids, intra-operative events and bloods loss will be taken from the anaesthetic chart kept by the clinical team and transcribed into digital format for analysis.

# Postoperative Day 1

## 10 Postoperative Blood Sampling

Participants will have an additional 4ml of blood taken in an EDTA vial at the time of their routine postoperative blood sampling the day following surgery. This will be transported to the School of Infection and Immunity at the University of Glasgow and centrifuged before being stored prior to analysis.

## 11 Postoperative Day 1 Delirium Assessment

Participants will be visited on the postoperative ward and assessed for the presence of delirium using the 4AT and Delirium Scale (DRS-R-98) administered by appropriately qualified assessors. Step 11 includes a Step case.

### Delirium

# Postoperative Day 3 +/- 1

step case

### Delirium

In the case that a participant develops postoperative delirium their clinical team will be informed. Their legal representative will also be informed and asked for consent to continue in the study on the participant's behalf.

## 12 Postoperative Day 3 Delirium Assessment

Participants will be visited on the postoperative ward and assessed for the presence of delirium using the 4AT and Delirium Rating Scale (DRS-R-98) administered by appropriately qualified assessors.

## Postoperative Day 5 +/- 1

### 13 Postoperative Day 5 Delirium Assessment

Participants will be visited on the postoperative ward and assessed for the presence of delirium using the 4AT and Delirium Rating Scale (DRS-R-98) administered by appropriately qualified assessors.

Step 13 includes a Step case.

#### Early Discharge

## 6 Month Postoperative Follow-Up

step case

### Early Discharge

In the case that a participant is discharged from hospital prior to the fifth postoperative day, data for delirium incidence will be censored at the last completed delirium assessment.

### 14 Six Month Follow-Up for Postoperative Cognitive Dysfunction

Six months following the date of surgery participants will be invited back, with their informants to an interview repeating the semi-structured interview, physical rating, cognitive testing, mental health assessment and short IQCODE to assess for change from baseline.

## Blood Sample Analysis

- 15 Stored serum samples will be prepared and analysed at the University of Glasgow School of Infection and Immunity using Luminex technology. Samples will be identifiable by participant number and whether pre- or post-operative. Samples will be analysed for concentrations of C-Reactive Protein (CRP), Interleukin 6 (IL-6), and Interleukin 1-beta (IL-1B).

## Statistical Analysis

### 16 Primary Outcome

The primary outcome of the study will be incidence of postoperative delirium as diagnosed by 4AT and DRS-R-98.

### 17 Secondary Outcome

The secondary outcome of interest will be incidence postoperative cognitive dysfunction as defined by a reduction in test score by one standard deviation, across two or more cognitive assessments.

## 18 Variables

Categorical variables will be expressed as percentage and continuous variables will be assessed for normality before being expressed as either a mean +/- standard deviation or a median and inter-quartile range as appropriate. Variables will be compared between cases and non-cases using Mann-Whitney U tests or chi-squared tests as appropriate.

## 19 Model Development

Generalised linear models will be used to analyse variables with respect to incidence of postoperative delirium and postoperative cognitive dysfunction in order to form prognostic models for these outcomes.