SDIM: Spinal Deformity Intraoperative Monitoring

Understanding and managing intraoperative neuromonitoring changes during spinal deformity surgery: a prospective interventional study

CLINICALTRIALS.GOV: NCT03880292

Statistical Analysis Plan

File name: SDIM_SAP_v2.docx

Version and date: Version 2.0, 12-Oct-2022

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1 Document Version History

Version	Publish Date	Description of Changes	Reason for Changes
1.0	04Oct2020	N/A	N/A
2.0	14Oct2020	Update to definition of cord and non-cord level events that precede an IONM alert.	Alerts could not be accurately categorised as having occurred after an event that is linked to the spinal cord.

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Abbreviations and definitions

CIP	Clinical Investigation Plan
EMG	Electromyography
FU	Follow-up
ICF	Informed consent form
IONM	Intraoperative neuromonitoring
LEMS	Lower extremity muscle score
MAP	Mean arterial pressure
MEP	Motor evoked potentials
SAP	Statistical Analysis Plan
SD	Standard deviation
SDIM	Spinal deformity intraoperative monitoring
SSEP	Somatosensory evoked potentials

Conventions

<defined term> Each time a term defined within this document has been referred to in the text, this has been highlighted by enclosing the definition within "less than" and "greater than" symbols.

<<definition>> The definition corresponding to each defined term has been enclosed in double "less than" and "greater than" symbols.

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PART A: Methods

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1 Introduction

1.1 Preface

Spinal deformity encompasses a broad spectrum of conditions leading to curvature of the spine, characterized by abnormal bending or flexure in the vertebral column [1]. Conservative management of spinal deformity is often not efficacious in treating severe deformity and does not prevent curve progression [2]. Patients with complex spinal deformities need specialized spinal surgeons alongside specialists in rehabilitation, pain control, physical medicine, and bracing and orthotics [3]. Intraoperative neuromonitoring (IONM) is a tool that provides real-time feedback of critical neurological pathways to surgical teams to help prevent or mitigate neurological injury during surgery [4]. This enhances safety of spinal surgery techniques by alerting surgical teams, who can then implement reversal manoeuvres to restore neuro signals above critical thresholds [5]. IONM uses a number of modalities, each with the purpose of detecting neurological responses that are out of range and, resultantly, provides an alert to the surgical team who can immediately perform corrective action. Currently, somatosensory evoked potentials (SSEP), transcranial motor evoked potentials (MEP), and electromyography (EMG) are used in spinal surgery for intraoperative assessment [4].

To date, there are no studies that prospectively collect real-time neuromonitoring data during spinal deformity surgery with sufficient information to determine incidence of neuromonitoring alerts by type, discriminate between intraoperative manoeuvres that can successfully reverse the changes, identify ineffective manoeuvres, determine the association between intraoperative factors and incidence of postoperative neurological deficits, or help establish warning criteria.

1.2 Scope of the analyses

These analyses will assess the incidence of IONM alerts, their association with neurological deficits, as well as the effect of intraoperative manoeuvres, and will be included in the Final Study Report.

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2 Study objectives and endpoints

2.1 Study objectives

Primary objective

The primary objective of this study will be to determine the incidence of IONM alerts in complex, high-risk spinal deformity surgeries and identify the events that lead to such alerts.

Secondary objectives

- To document intraoperative manoeuvres performed in response to alerts, and to determine their success rate in reversing neuromonitoring changes
- To determine the incidence of de novo postoperative neurological deficits and their association with:
  - alerts
  - successful manoeuvres
  - unsuccessful manoeuvres
- To determine risk factors of intraoperative neuromonitoring alerts
- To make an exploratory analysis of alert patterns and their relation to spinal cord syndromes

2.2 Endpoints

Primary endpoint

ID	Time Frame	Unit	Endpoint	Subgroup Analysis
1	Intraoperative	Patient	The incidence of IONM alerts	Modality combination

Secondary endpoints

<u>IONM count and frequencies</u>

ID	Time Frame	Unit	Endpoint	Subgroup Analysis
2	Intraoperative	Patient	The incidence of IONM alerts	High grade spondylolisthesis (Y/N) * Cord level
3	Intraoperative	Patient	The count of IONM alerts.	N/A
4	Intraoperative	Alert	The frequency of IONM Alerts	Modality combination

<u>IONM alert details and preceding events</u>

ID	Time Frame	Unit	Endpoint	Subgroup Analysis
5	Intraoperative	Alert	Minutes from incision	
6	Intraoperative	Alert	Minutes from preceding event	
7	Intraoperative	Alert	Blood pressure	
8	Intraoperative	Alert	Arterial pressure (MAP)	
9	Intraoperative	Alert	Haemoglobin	
10	Intraoperative	Alert	Degree of left SSEP signal loss at alert t=”0 mins”	
11	Intraoperative	Alert	Degree of right SSEP signal loss at alert t=”0 mins”	
12	Intraoperative	Alert	Degree of left MEP signal loss at alert t=”0 mins”	Each of the possible muscle group affected (12 binary subgroup variables).
13	Intraoperative	Alert	Degree of right MEP signal loss at alert t=”0 mins”	Each of the possible muscle group affected (12 binary subgroup variables).
14	Intraoperative	Alert	EMG activity	

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15	Intraoperative	Alert	EMG activity – muscle group(s)		
16	Intraoperative	Alert	EMG activity – duration		
17	Intraoperative	Alert	EMG activity at closure		
18	Intraoperative	Alert	MEP muscle group affected on the left side	= "None"	
19	Intraoperative	Alert		= "Abdominal (Adb)"	
20	Intraoperative	Alert		= "Psoas"	
21	Intraoperative	Alert		= "Adductors (Add)"	
22	Intraoperative	Alert		= "Rectus femoris (RF)"	
23	Intraoperative	Alert		= "Tibialis anterioris (TA)"	
24	Intraoperative	Alert		= "Abductor hallucis (AH)"	
25	Intraoperative	Alert		= "Hamstrings (Ham)"	
26	Intraoperative	Alert		= "Medial gastrocnemius (MG)"	
27	Intraoperative	Alert		= "Upper extremity (Upper Ext)"	
28	Intraoperative	Alert		= "Anal sphincter (Sph)"	
29	Intraoperative	Alert		= "Other"	
30	Intraoperative	Alert	MEP muscle group affected on the right side	= "None"	
31	Intraoperative	Alert		= "Abdominal (Adb)"	
32	Intraoperative	Alert		= "Psoas"	
33	Intraoperative	Alert		= "Adductors (Add)"	
34	Intraoperative	Alert		= "Rectus femoris (RF)"	
35	Intraoperative	Alert		= "Tibialis anterioris (TA)"	
36	Intraoperative	Alert		= "Abductor hallucis (AH)"	
37	Intraoperative	Alert		= "Hamstrings (Ham)"	
38	Intraoperative	Alert		= "Medial gastrocnemius (MG)"	
39	Intraoperative	Alert		= "Upper extremity (Upper Ext)"	
40	Intraoperative	Alert		= "Anal sphincter (Sph)"	
41	Intraoperative	Alert		= "Other"	
42	Intraoperative	Alert	Event preceding alert	= "Systemic"	
43	Intraoperative	Alert		= "Anaesthesia"	
44	Intraoperative	Alert		= "Technical"	
45	Intraoperative	Alert		= "Surgical cause"	- Exposure (Y/N) - Implant Placement (Y/N) - Osteotomy/Release (Y/N) - Correction/Rod Placement (Y/N) - Traction (Y/N) - Traction – Pre-incision (Y/N) - Traction – Pre-implant placement (Y/N) - Traction – Pre-Rod insertion (Y/N) - Traction – Post Rod insertion (Y/N) - Other (Y/N)
46	Intraoperative	Alert	Category of implant placement (Concave, Convex, Neutral) [Related to "Event preceding the alert" > "Surgical Cause" > "Implant Placement"]		
47-49	Intraoperative	Alert	Types of implant ("Screw", "Hook", "Wire") [Related to "Event preceding the alert" > "Surgical Cause" > "Implant Placement"]		
50-77	Intraoperative	Alert	Each implant level ("Occiput", "C1", etc.) [Related to "Event preceding the alert" > "Surgical Cause" > "Implant Placement"]		
78-105	Intraoperative	Alert	Osteotomy/release levels [Related to "Event preceding the alert" > "Surgical Cause" > "Osteotomy/Release"]		
106	Intraoperative	Alert	Osteotomy Type (1) [Related to "Event preceding the alert" > "Surgical Cause" > "Osteotomy/Release"]		
107-114	Intraoperative	Alert	Osteotomy Type (2) ("Decompression", "Decompression - Central", "Decompression - Concave side", "Decompression - Convex side", "Decompression – Posteriori body/disc", "Osteotomy closure", "Interbody placement", "Other")		

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[Related to “Event preceding the alert” > “Surgical Cause” > “Osteotomy/Release”]

Intraoperative manoeuvres in response to IONM alerts

ID	Time Frame	Unit	Endpoint	Subgroup Analysis
115-129	Intraoperative	Alert	Responses to alert ("Elevate BP", "Give Blood", … , "Other").	
130	Intraoperative	Alert	Wake up test on left leg	
131	Intraoperative	Alert	Wake up test on right leg	

Time to IONM signal recovery

- Signal recovery

  An MEP/SSEP signal that takes a value of “No Signal”, “0-25%”, or “25-50%” at any time point is considered as having a significant loss and is to be checked for recovery. A signal is considered to have recovered once it takes a value of “50-75%” or “75-100%” and all subsequent time points also take either of these two values.

  An EMG signal is considered to have recovered when, after EMG activity was indicated, there was no EMG activity at closure.

- Alert recovery

  An alert is considered as “Fully recovered” if all affected signals have recovered. An alert is considered as “Partially recovered” is at least one of the affected signals did not recover. An alert is considered as “Not recovered” if none of the affected signals recovered.

  Irrespective of whether an alert is partially or fully recovered, the time of the alert recovery is considered as the latest of the individual signal recovery times. Alerts with EMG activity but no significant MEP or SSEP loss are not applicable with regards to time of recovery.

ID	Time Frame	Unit	Endpoint		Subgroup Analysis
132	Intraoperative	Alert	Alert recovery		Modality combination
133	Intraoperative	Alert	Time of alert recovery		Modality combination
134	Intraoperative	Alert	Time of signal recovery for:	MEP Left	
135	Intraoperative	Alert		MEP right	
136	Intraoperative	Alert		SSEP left	
137	Intraoperative	Alert		SSEP right	
138	Intraoperative	Alert	Level of signal at recovery, or last known degree of signal loss, for:	MEP Left	
139	Intraoperative	Alert		MEP right	
140	Intraoperative	Alert		SSEP left	
141	Intraoperative	Alert		SSEP right	

ASIA lower extremity motor score (LEMS)

ID	Time Frame	Unit	Endpoint	Subgroup Analysis
142	Postop after anaesthesia	Patient	The ASIA lower extremity muscle score (LEMS)	
143	Discharge/30 days postop	Patient	The ASIA lower extremity muscle score (LEMS)	

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Sensory function

ID	Time Frame	Unit	Endpoint	Subgroup Analysis
144	Postop after anaesthesia	Patient	Left light touch	Lowest normal level
145	Postop after anaesthesia	Patient	Right light touch	Lowest normal level
146	Postop after anaesthesia	Patient	Left pin prick	Lowest normal level
147	Postop after anaesthesia	Patient	Right pin prick	Lowest normal level
148	Postop after anaesthesia	Patient	Root sensory abnormality?	Lowest normal level
149	Discharge/30 days postop	Patient	Left light touch	Lowest normal level
150	Discharge/30 days postop	Patient	Right light touch	Lowest normal level
151	Discharge/30 days postop	Patient	Left pin prick	Lowest normal level
152	Discharge/30 days postop	Patient	Right pin prick	Lowest normal level
153	Discharge/30 days postop	Patient	Root sensory abnormality?	Lowest normal level

De novo neurological deficits

ID	Time Frame	Unit	Endpoint	Subgroup Analysis
154	Baseline to postop	Patient	Decrease of at least one point from baseline	
155	Baseline to postop	Patient	Worsening of sensory function from baseline	
156	Baseline to postop	Patient	De novo spinal cord syndrome	

Pattern of signal loss

Pattern of signal loss (for MEP and SSEP) will be classified as outlined in Table 1 where '+' indicates an amplitude loss > 50% of baseline and '-' indicates a signal loss ≤ 50%. Table 1 also shows the possible corresponding cord syndrome for each pattern.

Table 1 – Pattern of signal amplitude loss from baseline and corresponding cord syndrome

			Pattern of signal loss			
Pattern	Description	Possible cord syndrome	MEP Left	MEP Right	SSEP Left	SSEP Right
A	Bilateral MEP Bilateral SSEP	Complete Cord Injury/central cord syndrome	+	+	+	+
B	Bilateral MEP No SSEP	Anterior Cord Syndrome	+	+	-	-
C	No MEP Bilateral SSEP	Posterior Cord Syndrome	-	-	+	+
D1	Unilateral MEP Unilateral SSEP	Brown Sequard Syndrome	+	-	+	-
D2			-	+	-	+
D3		N/A	-	+	+	-
D4			+	-	-	+
E1	Bilateral MEP Unilateral SSEP	N/A	+	+	+	-
E2			+	+	-	+
F1	Unilateral MEP Bilateral SSEP	N/A	-	+	+	+
F2			+	-	+	+
G1	Unilateral MEP	N/A	-	+	-	-

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G2	No SSEP		+	-	-	-
H1	No MEP Unilateral SSEP	N/A	-	-	-	+
H2			-	-	+	-

ID	Time Frame	Unit	Endpoint	Subgroup Analysis
157	Intraoperative	Alert	The signal loss pattern as defined in Table 1.	Alert time * High grade spondylolisthesis (Y/N) * Cord level
158	Intraoperative	Alert	The signal loss pattern at time=0.	High grade spondylolisthesis (Y/N) * Cord level AND: - EP=SYS - EP=ANE - EP=TECH - EP=SURG - EP=SURG and Exposure (Y/N) - EP=SURG and Implant Placement (Y/N) - EP=SURG and Osteotomy/Release (Y/N) - EP=SURG and Correction/Rod - EP=SURG and Placement (Y/N) - EP=SURG and Traction (Y/N) - EP=SURG and Other (Y/N).
159	Intraoperative	Alert	Whether a change of signal pattern loss has occurred.	High grade spondylolisthesis (Y/N) * Cord level
160	Intraoperative	Alert	Whether a change of signal pattern loss has occurred.	High grade spondylolisthesis (Y/N) * Cord level AND: Each possible response to the alert.
161	Intraoperative	Alert	The specific type of change in the signal pattern loss.	High grade spondylolisthesis (Y/N) * Cord level

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3 Study methods

3.1 General study design

This study will be a prospective, interventional, multicentre case series study. There will be no blinding or treatment allocation conducted within this study. All patient treatments are per standard of care based on the discretion of the treating doctor at each participating site. Study-related interventions are limited to:

- Standardisation of the IONM protocol
- Standardisation of the threshold for IONM alerts
- Documentation in real time of IONM alerts and manoeuvres made before and in response to alerts
- Standardization of the timepoints for the neurological assessments

Patients included in this study require spinal surgery and IONM is part of the standard of care regardless of their participation. Neurological assessments are also part of the normal follow-up (FU) routine of these patients, but the standardization of the timepoints ensures the proper documentation of the neurological status and comparability.

All patients with a signed written informed consent form (ICF) will be allocated to a unique patient trial number. All patients who commence treatment within the study are considered as enrolled. All enrolled patients should be followed up within the study, except if their study participation is prematurely terminated. The recruitment period will be up to 24 months, during which at least 550 patients are planned to be enrolled.

3.2 Timing of assessments

Table 2: Study schedule

Assessments	Pre-, intra- and postoperative visits			
	Visit 1	Visit 2	Visit 3	Visit 4
	Screening/ preoperative	Intraoperative (day 0)	Postoperative (immediately after anaesthesia reversal)	Postoperative (day 30/discharge*)
Patient information/consent	X			
Eligibility	X			
Baseline characteristics	X			
Surgical details		X		
Alert details and preceding events		X		
Intraoperative maneuvers in response to alerts		X		
Time of IONM signal recovery		X		
ASIA LEMS	X		X	X
Sensory function	X		X	X

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Assessments	Pre-, intra- and postoperative visits			
	Visit 1	Visit 2	Visit 3	Visit 4
	Screening/ preoperative	Intraoperative (day 0)	Postoperative (immediately after anaesthesia reversal)	Postoperative (day 30/discharge*)
Spinal cord syndrome			X	X
Neurological deficits de novo			X	X**
Radiological parameters	X			X

* Whichever occurs first
** First standing radiographic outcome after surgery

3.3 Definitions

- The <<reference date>> for assessment of timing of FU assessments and events will be defined as date of surgery. FU time of visit 4 will be calculated as <assessment date> – <reference date>.
- <<Data entered>>, <<Written informed consent>>, <<Eligible>>, <<Dropout>>, and <<Death>> will be defined according to the Standard Formula Calculation procedure (SOP 03.050).
- <<Enrolled>> will be defined as a patient who signed the informed consent.
- <<Assessed for primary outcome>> will be defined as a <enrolled> patient who underwent surgery with IONM according to the predefined intraoperative IONM protocol.

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4 Sample size

With an enrolment period of 2 years, it is expected that data from at least 550 patients will be collected. This is based on the anticipated number of cases seen within the timeframe at the sites, accounting for a proportion of patients' refusing to provide consent, drop-outs, and loss to FU. This sample size will adequately provide enough events to conduct a logistic regression model of potential predictors of alerts, as a general rule of thumb is that one independent variable can be included for every ten events. We hypothesize that IONM alerts will occur in at least 100 patients over the course of the study, allowing for the analysis of ten potential predictors in the regression model. Missing values in predictors will reduce the number of usable patients.

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5 General considerations

5.1 Timing of analysis

A comprehensive final analysis will be conducted following the completion of the FU for at least 550 patients. All activities specified in the Data Management Plan will be completed and the database locked prior to completion of the final tables, listings, and figures (including finalization of this SAP).

5.2 Analysis populations

Two analysis populations will be defined for this study. Any intended deviations from these definitions will be defined, justified, and documented prior to the final study analysis, and before any analysis by treatment allocation is produced (see (Blind) Data Review, SOP 03.055).

5.2.1 Enrolled Set (ENR)

The enrolled set includes all patients who provided a signed ICF and were entered in the database.

This set will be used for the subject disposition tables and listings.

5.2.2 Safety Set (SAF)

The safety set contains subjects from ENR who are 1) eligible, 2) in whom the planned surgery (at least one of the three eligible surgical indications) is conducted, and 3) in whom the IONM is done per our protocol without interferences.

The above definition will be derived using the following rules:

- Eligibility will be assessed as all subjects in the ENR who signed the informed consent on or before 31-MAR-2022 and passed all inclusion/exclusion criteria.
- The three eligible indications will be checked in the enrolment form under section 2.4.1.
- The subjects who were treated with the IONM alert system per protocol and without interferences as those who did not drop out according to their dropout form.

This set will be used for all primary and secondary related listings and tables.

5.3 Covariates and subgroups

Covariates

N/A

Subgroups

The following subgroups will be applied to the relevant endpoints as specified in section 2.2.

- ***Modality Combination***

  The modality combination of an alert indicates the relevant neuromonitoring modality of the alert in question. For the MEP and SSEP signals, a significant loss (“No Signal”, “0-25%”, or “25-50%”) at any of the recorded time points indicates that the modality is affected. For EMG, an indication of EMG activity is sufficient to indicate relevance.

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The modality combination of an alert can take the following values:
- MEP only
- SSEP only
- EMG only
- MEP and SSEP only
- MEP and EMG only
- SSEP and EMG only
- MEP and SSEP and EMG

- ***Cord level***

  The cord-level of an alert is defined with the following criteria:

  - In all subjects, alerts fulfilling the following criteria are considered to identify cord-level alerts:
    1. On the alert form:
       - If Q3.1.2 (If surgical cause:) answers Exposure, the level is unclear and should be derived from additional information (if available).
       - If Q3.1.2 (If surgical cause:) answers Implant Placement, the level is indicated in Q3.2.3 (Implant levels). If Q3.2.3 answers T12 or above, then it is cord level.
       - If Q3.1.2 (If surgical cause:) answers Implant Placement, the level is indicated in Q3.2.3 (Implant levels). If Q3.2.3 answers L1 or below, then it is non-cord level.
       - If Q3.1.2 (If surgical cause:) answers Osteotomy/Release, the level is indicated in Q3.3.1 (Osteotomy/release levels). If Q3.3.3 answers T12 or above, then it is cord level.
       - If Q3.1.2 (If surgical cause:) answers Osteotomy/Release, the level is indicated in Q3.3.1 (Osteotomy/release levels). If Q3.3.3 answers L1 or below, then it is non-cord level.
       - If Q3.1.2 (If surgical cause:) answers Correction/Rod Placement, then the spinal cord level can be found on the demographics form (see point 2.).
       - If Q3.1.2 (If surgical cause:) answers Traction, the level is always cord level.
       - If Q3.1.2 (If surgical cause:) answers Other, the level is unclear and should be derived from the additional information (if available).
    2. On the demographics form:
       - If the surgical cause on the alert form is Correction/Rod Placement (Q3.1.2), then the primary diagnosis should be checked on the demographics form (Diagnosis Q1). If Q1 answers Scoliosis, Coronal apex (Radiological Parameters Q2.1) should be checked. If Q2.1 answers T12 or above, then it is cord level.

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- If the surgical cause on the alert form is Correction/Rod Placement (Q3.1.2), then the primary diagnosis should be checked on the demographics form (Diagnosis Q1). If Q1 answers Scoliosis, Coronal apex (Radiological Parameters Q2.1) should be checked. If Q2.1 answers L1 or below, then it is non-cord level.
- If the surgical cause on the alert form is Correction/Rod Placement (Q3.1.2), then the primary diagnosis should be checked on the demographics form (Diagnosis Q1). If Q1 answers Kyphosis, Sagittal apex (Radiological Parameters Q2.2) should be checked. If Q2.2 answers T12 or above, then it is cord level.
- If the surgical cause on the alert form is Correction/Rod Placement (Q3.1.2), then the primary diagnosis should be checked on the demographics form (Diagnosis Q1). If Q1 answers Kyphosis, Sagittal apex (Radiological Parameters Q2.2) should be checked. If Q2.2 answers L1 or below, then it is non-cord level.

- ***Spondylolisthesis vs. non-spondylolisthesis***

  Patients will be divided into two subgroups of spondylolisthesis vs. non-spondylolisthesis based on the primary diagnosis. If the primary diagnosis of the patient is High grade spondylolisthesis, the patient is categorized as in the spondylolisthesis subgroup; the remaining patients will be categorized as in the non-spondylolisthesis subgroup.

5.4 Missing data

For “Time to IONM signal recovery” and “Pattern of signal loss” endpoints:

> With regards the value of MEP and SSEP signals recorded in section 6.1-6.7 of the eCRF, a Last Observation Carried Forward (LOCF) approach will be used to impute data for analysis of endpoints. This will only be applied when the observation being carried forward takes the value “50-75%” or “75-100%”, otherwise it will be kept as a missing value. Signals that are completely missing across section 6.1-6.7 are assumed to take the value 75-100%.

In general, some degree of missing data is expected for both baseline characteristics and outcomes for this study. However, since no bias to the outcomes is expected, no imputation will be employed outside of the aforementioned.

5.5 Interim analyses and data monitoring

There is no interim analysis planned for this study.

5.6 Multicentre studies

This is a multicentre study conducted at 21 clinics from 13 countries. The relatively small recruitment targets per site would make site-specific analysis impractical. Summary statistics will be produced according to study centre for patient inclusion and disposition characteristics (i.e. inclusion/exclusion criteria, dropouts), but not for subsequent outcomes.

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5.7 Multiple testing

This study is not confirmatory and no formal hypothesis will be tested. Therefore, no correction for multiple testing is needed.

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6 Protocol deviations

Protocol deviations technically include issues relating to i) eligibility and consent, ii) treatment compliance, iii) dropout from FU, and (d) visits punctuality. The summaries described in this section will provide the information required to produce a flow diagram for the Final Study Report, and will generally be referred to as "Patient disposition summaries". The flow diagram will be produced by the Medical Writer assigned to the study.

6.1 Eligibility and consent

The first patient disposition summary will provide details of all patient exclusions. The summary will first be split into "Ineligible" and "Eligible" patients. "Ineligible" patients will be further broken down into "Patients failing inclusion criteria", and "Patients meeting exclusion criteria". Frequencies and percentages will be included for each category. Each patient will be allowed to contribute to more than one category.

Patients without signed ICF will be excluded from any analysis population. Patients who withdrew ICF will be censored at the time of withdrawal.

6.2 Patient dropout and visit completion

Ideally the patient disposition summaries should not only clarify the number of patients contributing to each of the analysis populations at baseline, but also at the time of each of the scheduled FU assessments. Additional summaries are therefore required to provide details of the reason and timing for any patient dropouts. The timing of dropout and its impact on visit completion cannot be summarized in a single table, as this table would have to include multiple assessment times, and multiple visit completion categories.

- First, a summary will be produced detailing the number of patients who dropped out during the defined period of study FU, and the coded reason for dropout. This summary will be done for the <full analysis population> and by study centre. A listing will provide details of the specific patients and any description of reasons for dropout.
- Second, summaries will be produced detailing the completion status of patients at the time of each scheduled FU assessment.
    - Each scheduled assessment should be assigned to one of the completion categories "Done", "Missing", "Dropout" and "Death" according to AO ITC SOP 03.050 "Standard Formula Calculation". Then the frequency and percentage of patients in every completion category should be calculated for each visit; this calculation corresponds to the "overall FU rate" described in the SOP. The overall FU rate summary should be produced for the <full analysis population>.
    - The summary will then be repeated including only the "Done" and "Missing" categories, and with percentages calculated using the sum of these two categories as the denominator; this will correspond to the "compliance FU rate" described in the SOP. The compliance FU rate summary needs to be produced for the safety set (SAF), and simply gives an overall impression of compliance with FU, independent of patient dropout and death.
    - A listing will provide details of patients with missing visits, plus any related reasons or comments

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7 Summary of study data

Baseline characteristics and outcomes recorded at scheduled FU assessments will be presented using simple summary statistics. Categorical variables will be summarized using frequency and percentage for each category. Continuous variables will be summarized using mean, standard deviation (SD), median, inter-quartile range, and minimum and maximum values. In general, continuous variables with both baseline and FU measurements available will also be summarized in terms of the individual patient-level changes between baseline and follow-up. All summary tables will be annotated with the total population size relevant to that table, including any missing observations.

7.1 Demographic and baseline variables

Baseline characteristics are listed in CIP Section 6.1 and include demographics, medical history, surgical indication, primary diagnosis, diagnosis subtype, pre-operative neurological status (ASIA LEMS, sensory function) and radiological parameters. Baseline characteristics will be presented for the safety set (SAF).

7.2 Surgery and anaesthesia details

Surgery details are listed in CIP Section 6.2.

7.3 IONM details

IONM details are listed in CIP Section 6.2.3 and include information on IONM modality (CIP Section 6.2.3.1) and IONM signals at baseline (CIP Section 6.2.3.2).

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8 Statistical analyses

There is no formal hypothesis to this study. The study aims to provide insights to the incidence of neuromonitoring alerts and their association with neurological deficits.

All variables will be listed by subject and, where appropriate, by visit. IONM alert variables will be listed by subject and, where appropriate, by alert. Data will be summarized as described in Section 7. Primary and secondary objectives will be analysed on the safety set (SAF).

8.1 Primary analysis

The primary analysis for this study will consist of descriptive statistics pertaining to the incidence of IONM alerts.

8.2 Secondary analyses

The secondary analysis will present the frequency and percentage (of the analysis set in question) of each categorical endpoint and summary statistics for each continuous endpoint.

Additionally, the following analyses will be performed:

1. Sensitivity and specificity of the alerts to detect neurological deficits using a minimum threshold of 50% change of the signal where the presence of post-operative de novo deficits are used as the "gold standard" [6].
2. Association between neurological deficit and intra-operative alerts (on patient level) will be evaluated using the chi-squared test at significance level 0.05.

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9 Safety analyses

As the study-related risks are considered minimal (see CIP Section 8.1) and all patients will be treated as per standard of care of the hospital, no (serious) adverse events will be collected. Only neurological complications are collected as one of the main outcomes of the study.

9.1 Extent of exposure

Not applicable.

9.2 Adverse events

Adverse events will not be collected in this clinical investigation. Only neurological complications are collected as one of the main outcomes of this study.

9.3 Deaths, serious adverse events, and other significant adverse events

A summary of deaths will be reported, including deaths related to treatment failure.

9.4 Pregnancies

Not applicable.

9.5 Clinical laboratory evaluations

Not applicable.

9.6 Other safety measures

Not applicable.

10 Other analyses

Not applicable.

11 Reporting conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as “<0.001”.

12 Technical details

This SAP was prepared with reference to the following document:

- SDIM_CIP_v1.0.docx dated 12-Dec-2018

Source data:

All patient data will be stored in a bespoke REDCap electronic data capture database.

Software:

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The statistical analyses will be performed using the software SAS 9.4 or higher.

Quality assurance:

A second review statistician will independently perform quality control and consistency checks of the analysis outputs. The reviewing statistician will have an overview of the entire analyses and will explicitly check the code producing tables and listings as well as any other pieces of code as desired.

13 Summary of changes to the protocol

The analysis will be performed as planned in the CIP except for the following changes:

- The wording "causative event" has been replaced by "preceding event" throughout this SAP since the causality might not always be apparent.
- SSEP/MEP signal loss is measured as categorical variable in this study; therefore "as percentage" has been replaced by the appropriate categories.
- "De novo neurological deficits" have been added as secondary endpoints.
- Surgical indications have been added as potential subgroups for analysis.

14 References

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PART B: Shell tables, listings and figures

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3 Table Templates

Table xx: Title

<Analysis set X> *(e.g., Enrollment set, Safety analysis set)*

Neuromonitoring parameters	Category	Patients/Alerts (N=xx)
Monitoring modalities used (SSEP)	Not used	xx (xx%)
	Used	xx (xx%)
Monitoring modalities used (MEP)	Not used	xx (xx%)
	Used	xx (xx%)
Monitoring modalities used (EMG)	Not used	xx (xx%)
	Used	xx (xx%)
Type of anesthesia	TIVA	xx (xx%)
	MAC	xx (xx%)
	Other	xx (xx%)
	Missing	xx
…	…	…

<Insert footnote if needed>

Note: This is a template table for categorical variables (e.g. main reason for dropout, type of anesthesia and etc.).

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Table xx: Title

<Analysis set X>

Variables	Statistics	Patients/Alerts (N=xx)
Gender	Female	xx (xx%)
	Male	xx (xx%)
	Missing	xx
Height[cm]	n	xx
	Missing	xx
	Mean (SD)	xx (xx)
	CV	xx
	Min	xx
	Median	xx
	Max	xx

<Insert footnote if needed>

Note: This is a template table for continuous and categorical variables (e.g., gender, height, weight and etc.).

For continuous variables (e.g., height, weight), a summary of key statistics will be provided. For categorical variables (e.g., gender), a frequency number and percentage will be provided.

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Table xx: Title

<Analysis set X>

Subgroup	Category	Statistics	Patients/Alerts (N=xx)
Subgroup label	Subgroup category 1 label	n	xx
		nmiss	xx
		Mean (SD)	xx (xx)
		CV	xx
		Min	xx
		Median	xx
		Max	xx
	Subgroup category 2 label	n	xx
		nmiss	xx
		Mean (SD)	xx (xx)
		CV	xx
		Min	xx
		Median	xx
		Max	xx

<Insert footnote if needed>

Note: similar to previous tables but adding “visit” when necessary.

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