SDIM: Spinal Deformity Intraoperative Monitoring

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

Clinical Investigation Plan

File name: SDIM_CIP_v1.0.docx

Version and date: Version 1.0 12-Dec-2018

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Abbreviations/glossary

Abd	Abdominal rectus
Add	Adductors
AH	Abductor hallucis
AIS	American Spinal Injury Association (ASIA) Impairment Scale (AIS)
ASIA	American Spinal Injury Association
AE/SAE	Adverse event(s)/serious adverse event(s)
ALIF	Anterior lumbar interbody fusion
AO	Arbeitsgemeinschaft für Osteosynthesefragen = Association for the Study of Internal Fixation (ASIF)
AOCID	AO Documentation and Publishing Foundation, Clinical Investigation and Documentation
BAEP	Brainstem auditory evoked potentials
BIS	Bispectral index monitor
CIP	Clinical investigation plan
CMAPs	Compound muscle action potentials
CRA	Clinical research associate
CRO	Contract research organization = clinical research organization
CSA	Compressed spectral array
DF	Dorsiflexors
DLIF/XLIF	Direct lateral interbody fusion/extreme lateral interbody fusion
DSMB	Data safety monitoring board
EC	Ethics committee
eCRF	Electronic case report form
EEG	Electroencephalography
EMG	Electromyographic
EDC	Electronic data capture
EP	Evoked potential
FDA	Food and Drug Administration
Free run	Free running
FSR	Final study report
FU(s)	Follow-up(s), eg follow-up visit(s), follow-up procedure(s)
GCP	Good Clinical Practice
Ham	Hamstrings
HF	Hip flexor
Hz	Hertz
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IONM	Intraoperative neuromonitoring
IRB	Institutional review board
ISF	Investigator site file
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
ISO	International Organization for Standardization
ITT	Intention to treat
LEMS	Lower extremity motor score
MAC	Minimal alveolar concentration
MeSH	Medical subject heading
MEP	Motor evoked potentials
MG	Medial gastrocnemius
MIOM	Multimodal intraoperative monitoring
ms	Milliseconds
NLI	Neurological level of injury

NMEP	Neurogenic motor evoked potentials
OLIF	Oblique lateral interbody fusion
PCI	Principal coordinating investigator (= principal clinical investigator)
PCO	Posterior column osteotomy
PF	Plantar flexor
PI	Principal investigator
PLIF	Posterior lumbar interbody fusion
PM	Project manager
PP	Per protocol
PSO	Pedicle subtraction osteotomy
Ptn	Tibial
pRBC	Packed red blood cells
Psoas	Iliopsoas
QM(S)	Quality management (system)
RF	Rectus femoris
SAP	Statistical analysis plan
SC	Study coordinator
SCI	Spinal cord injury
SD	Standard deviation
SDIM	Spinal deformity intraoperative monitoring
SDV	Source data verification
SI	Sub-investigator
SCV	Site close-out visit
SIV	Site initiation visit
SO	Safety officer
SOP	Standard operating procedure
Sph	Anal sphincter
SSEP	Somatosensory evoked potentials
Stim	Stimulated
TA	Tibialis anterioris
TIVA	Total intravenous anesthesia
TLIF	Transforaminal lumbar interbody fusion
Uln	Ulnar
Upper Ext	Upper extremity

Definitions

Baseline	Status pretreatment
Discharge	Discharge from orthopedic/trauma department
Eligible	Patients who were screened and meet all the inclusion and none of the exclusion criteria
Enrolled	Eligible patients with written informed consent who commenced treatment within the study (ie who had spinal deformity surgery)
Follow-up visit	FU; visit at predefined times after the treatment day
Follow-up population	Patients intended to be followed-up (ie enrolled population)
Treatment day	"Day 0"; day of operation
Written informed consent	Legally binding signature on the informed consent form (ICF) (ie either the patient, legally authorized representative or consultee), whereas the person who signs the ICF • has the ability to understand the content of the patient information has signed and dated the EC/IRB approved written informed consent

1 Synopsis

Official title	Understanding and managing intraoperative neuromonitoring changes during spinal deformity surgery: a prospective interventional study
Short title	SDIM
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Registration	ClinicalTrials.gov: NCT03880292
Background and purpose	With increased complexity and risk associated with the current treatment of spinal deformities, intraoperative multimodality monitoring has become a key component of the surgical procedures. While changes in neuromonitoring are frequent in osteotomy procedures (reports up to 75%) [1], recognizing and performing appropriate real-time operative maneuvers can help prevent and/or reverse serious neurological injury. Improving the surgical team's recognition and understanding of relevant intraoperative neuromonitoring changes can greatly improve outcome in spinal deformity surgery. Neuromonitoring research, to date, has been retrospective and has failed to fully correlate all important known factors. Prospectively collecting real-time data eliciting the key known contributing factors that lead to the changes, the actions taken, and the monitoring and clinical sequelae is needed. This will help fill significant knowledge gaps and have a significant impact on clinical practice in complex spinal surgeries.
Clinical condition	Spinal deformity and high-grade spondylolisthesis correction
Intervention/procedure investigated	Multimodal neuromonitoring with electromyography (EMG), somatosensory evoked potential (SSEP), and motor evoked potentials (MEP)
Comparison	N/A
Research type	Interventional
Research design	Prospective, case series, multicenter

Short description	A multicenter, international prospectively collected patient cohort undergoing high-risk spinal cord level surgery or spinal osteotomy procedures will be enrolled to establish the incidence of intraoperative alerts in high-risk spinal cord cases, and explore factors associated with mitigating injury. Baseline, intraoperative, and postoperative characteristics, including demographics, radiological features, lower extremity motor score (LEMS), procedure, anesthetic agents used, and baseline blood pressure will be recorded for either adult patients or pediatric patients. If a major change occurs in the intraoperative neuromonitoring, defined as a loss of amplitude greater than 50% in the MEP or SSEP from baseline or sustained EMG activity, a separate form (Appendix 3, Intraoperative Alert Form) will be completed in real-time by the neuromonitoring technician outlining the timing of the alert, blood pressure at the time, surgical events at the time of the change, intraoperative maneuvers performed to address the change, and resultant outcome of these maneuvers to address the neuromonitoring change. For each alert occurring during the procedure, a separate form will be completed. Once the patient is awake from anesthesia, the treating surgeon will perform a neurological examination to identify details about the deficit including sidedness, LEMS, sensory deficit, injury to the nerve root, incomplete spinal cord (ie anterior cord, posterior cord, central cord, Brown-Sequard), complete spinal cord injury, conus or cauda equina deficit. The examination is repeated on the day of discharge from hospital, or at day 30, whichever comes first and documented in the corresponding form. The objective of this study is to identify the incidence of intraoperative alerts in high-risk spinal cord cases, correlate significant neuromonitoring changes to intraoperative events, and identify maneuvers that will restore the neuromonitoring changes to baseline. The information provided by this study will educate spinal surgeons to recognize a spinal cord at risk and to perform intraoperative maneuvers that will decrease the incidence of neurological injuries.
Primary objective	To determine the incidence of intraoperative neuromonitoring alerts in complex, high-risk spinal deformity surgeries and identify the events that lead to such alerts.

Secondary objectives	• To document intraoperative maneuvers 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 maneuvers
	  - unsuccessful maneuvers
	• To determine risk factors of intraoperative neuromonitoring alerts
	• To make an exploratory analysis of alert patterns and their relation to spinal cord syndromes

Hypothesis	There is no formal hypothesis

Primary outcome measures	• Number of intraoperative neuromonitoring alert, defined as a major change in neuromonitoring signals:
	  ○ SSEP: amplitude loss > 50%
	  ○ MEP: amplitude loss > 50% in two of three muscle groups and/or
	  ○ EMG: sustained activity for > 10 seconds

Secondary outcome measures	Intraoperative monitoring alerts
	• Degree of change in the monitoring signals (SSEP, MEP, EMG)
	• Event preceding an alert
	• Timing of alert
	• Sensitivity and specificity of the alerts using a minimum threshold of 50% change in the neuromonitoring signal
	
	Success rate of reversal maneuvers to restore signal above the threshold
	• Number and type of maneuver(s) in response to an alert
	  ○ number and type of successful maneuvers
	  ○ number and type of unsuccessful maneuvers
	  ○ timing and degree of signal recovery in MEP and SSEP relative to baseline (as percentage)
	  ○ timing to restoration of baseline signal
	
	Neurological status
	• ASIA LEMS
	• Sensory function
	• Spinal cord syndromes
	
	Neurological alerts predictors, patterns and relationship to outcome
	• Predictors of neuromonitoring alerts
	• Identification of alert patterns
	• Association between neurological deficit and alert

Statistical considerations and estimated enrollment	With an enrolment period of two years, it is expected that data from at least 550 patients will be collected. In addition to determining the incidence of alerts, different analyses will be conducted to explore relationships between events that trigger an alert, maneuvers in response to an alert, and clinical outcome. This minimum number of patients is expected to allow identifying ten predictors of neuromonitoring alerts in patients undergoing high-risk spinal cord level surgery when entered into a multivariable prognostic model. Selection of the study parameters to enter in the final multivariable prognostic model will be done according to a first univariable analysis and/or principal component analysis. Based on Cohen's approach (ten events needed for each potential predictor), this study would require 100 patients experiencing intraoperative neuromonitoring alerts with complete data on predictors.

Start of enrollment **Last patient/last visit**	May 2019 (estimated) Sep 2021 (estimated)

Eligibility inclusion criteria	• Age ≥10 years to ≤80 years
	• Neurologically intact spinal cord (with or without radiculopathy)
	• Undergoing primary or revision procedure in the spine
	• Anterior and/or posterior surgical approach for any of the following:
	  ○ Correction of spinal deformity with a major Cobb angle of ≥ 80° in the coronal or sagittal plane
	  ○ Correction of high grade spondylolisthesis (Grades 3-5)
	  ○ Posterior column or 3-column osteotomy
	• Requiring multimodal neuromonitoring with EMG, SSEP, and MEP as per standard of care
	• Informed consent obtained for patients i.e.:
	  ○ Ability to understand the content of the patient information
	  ○ Willingness and ability to participate in the clinical investigation according to the Clinical Investigation Plan (CIP)
	  ○ Signed and dated EC/IRB approved written informed consent
	
	OR
	  ○ Written consent obtained according to defined and IRB/EC approved procedures for patients who are not able to provide independent written informed consent

Eligibility exclusion criteria	Preoperative exclusion criteria: • Neurodegenerative disease • Upper motor neuron lesion • Growing rods or growth guidance procedures • Tether or staple procedures • Stand-alone cervical deformity correction procedures • Any not medically managed severe systemic disease • Recent history of substance abuse (ie recreational drugs, alcohol) that would preclude reliable assessment • Pregnancy or women planning to conceive within the study period • Prisoner • Participation in any other medical device or medicinal product study that could influence the results of the present study
Study sites	15-20 clinics from 8-12 countries A detailed list of all study sites is provided separately.
Health authority	ECs/IRBs Health ministries/regulatory authorities/competent authorities

Pubmed Medical Subject Heading [MeSH] terms and keywords	• Spinal osteotomy • Spinal deformities • Intraoperative neuromonitoring • Somatosensory evoked potentials • Motor evoked potentials • Electromyography • Spinal cord injury
Monitoring and administration	All sites will receive the required documentation and will be trained and initiated formally by the sponsor/CRO. Administrative support will be established for all study sites and quality control measures will be implemented to ensure adequate data quality.
Data Safety Monitoring Board	This study will be part of standard intraoperative patient care with no applicable issues related to data safety monitoring
Imaging review	Radiographic images will be reviewed by the site at the time of surgery. Relevant measurements related to the imaging will be recorded on the datasheet.

2 General information/responsibilities

The International Council for Harmonisation for Good Clinical Practice (ICH-GCP) and ISO 14155 guidelines define the responsibilities of the sponsor, investigators, and CRA in the context of clinical investigations and are applicable for this research project. Specific topics, such as the permission from the responsible EC or IRB, are defined separately in the CIP. The study sites undertake to guarantee correct and prompt implementation, documentation, and transmission of the study data to the monitor.

The Principal Investigator (PI) and research team are instructed and trained about the conduct of the study by AOCID prior to the start of enrollment in order to verify their capability to cope with the required quality standards and compliance with the relevant standard operating procedures (SOPs). The Investigator Site File (ISF) containing all relevant study documents (ie essential documents) is provided to each clinic and needs to be kept up to date during the study period.

In the context of the study, the participating study sites will return the completely documented cases. Completely documented means that all FU visits have been carried out for the cases included in the study and that these assessments are recorded on the electronic Case Report Forms (eCRFs) specially designed for this study. The PI at each study site signs a corresponding investigator contract, where all relevant aspects (legal, financial, etc) are specified.

2.1 Responsibilities

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2.2 Study sites and investigators

Participating study sites and investigators are listed in a separate document. A maximum number of 15-20 clinics from 8-12 countries will be selected to achieve the target sample size.

3 Background and literature review

3.1 Definition and epidemiology

Spinal deformity encompasses a broad spectrum of conditions leading to curvature of the spine, characterized by abnormal bending or flexure in the vertebral column [2]. The prevalence of spinal deformity has been reported to be as high as 32%, with scoliosis being the most common spinal deformity reported [3]. Like other prevalent musculoskeletal disorders, spinal deformity is costly to manage, affects all ages and socioeconomic groups, and is a key contributor to disability and loss of productivity [4]. Spinal deformity also has a significant and measurable impact on health-related quality of life, including pain, function, self-image, mental health, work status, and disability [5]. The true burden of spinal deformity is difficult to estimate because not all persons with spinal deformity seek medical care.

3.2 Treatment Options

Conservative management of spinal deformity is often not efficacious in treating severe deformity and does not prevent curve progression [3]. Conservative therapies include rehabilitation, pain control, physical medicine, bracing, and orthotics. The decision to undergo conservative treatment and how it may be tailored are dependent on the patient's age, lifestyle, progression of deformity, extent of neurocompromise, pain, functional limitation, comorbidities, as well as perception of appearance. Patients with complex spinal deformities need specialized spinal surgeons alongside specialists in rehabilitation, pain control, physical medicine, and bracing and orthotics [6].

3.2.1 Pediatric Treatment

Conservative treatment of pediatric spinal deformity including bracing, orthotics and physical therapy, is typically recommended for patients with a curve magnitude less than 25 degrees [7]. In general, pediatric spinal deformity surgery is considered safe, with low reported rates of morbidity and mortality [8, 9]. Factors that determine the use of conservative or surgical treatment in pediatric populations include: female sex, younger age, and greater curve magnitude at diagnosis.

3.2.2 Adults

The management of adult spinal deformity is complex and typically begins with conservative treatment with the goals of reducing pain and improving function [3]. In severe cases of adult spinal deformity, surgery is considered, but surgical treatment of adult deformity is associated with a high complication rate and poor bone quality following surgical management [10, 11]. Operative treatment is indicated following failure of conservative treatment, severe back and leg pain, severe functional limitations, under 65 years of age.

3.2.3 Elderly Populations

In elderly patients with multiple risk factors and comorbidities, surgeons often consider nonoperative methods instead of surgical procedures to avoid serious complications in surgery. A multicenter study comparing spinal deformity surgery in three different age groups found that patients 65-85 years of age experiences 4.5 times the number of complications compared to patients in younger age groups [12]. Recently, two large multicenter trials confirmed complication rates after spinal surgery to be high, with a 30-day complication rate of 10.0%, mortality rate of 0.15%, a morbidity rate of 8.4%, reoperation rate of 3.7%, readmission rate of 3.9% and patients with comorbidities to be at the highest risk [8, 9].

3.3 Neuromonitoring and reducing rates of complications

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 [13]. This enhances safety of spinal surgery techniques by alerting surgical teams, who can then implement reversal maneuvers to restore neuro signals above critical thresholds [14]. 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. These modalities include motor evoked potentials (MEPs), somatosensory evoked potentials (SSEPs), electromyography (EMG), electromyography, brainstem auditory evoked potentials (BAEPs), and visual evoked potentials (VEPs) [15]. IONM, therefore, provides a safety measure for patients and surgeons by providing real time assessment of neurological function. Currently, SSEPs, transcranial motor evoked potentials (MEPs), and EMGs are used in spinal surgery for intraoperative assessment [13].

The evidence surrounding the benefits of intraoperative neuromonitoring is inconclusive. While some studies report that spinal deformity surgeries that incorporate neuromonitoring result in 50% lower neurological deficits [16], other studies have reported that modern IONM is less accurate with falling rates of efficacy [13, 17]. For example, a detailed literature search conducted surrounding the sensitivity and specificity of neurophysiologic monitoring during spinal surgery reports sensitivity ranges from 0% to as high as 100% and specificity ranging from 84% to 100% [13]. Some of this discrepancy surrounds environmental conditions and factors under which spinal surgeries take place, the types of alerts generated during surgery, and the type of monitoring conducted. For example, there is evidence that SSEP is broadly available, allows continuous monitoring, and useful for neuromuscular blockade, but has low sensitivity for motor deficit, evoked responses are sometimes delayed, and alerts remain unchanged with anterior spinal artery injury. MEP has sensitivity for motor deficits nearing 100% but does not allow for continuous monitoring and is highly sensitive to anesthetic effects. EMG is sensitive to nerve root injury, provides constant feedback, is useful in minimally invasive surgery, and easy to perform, but there is a high rate of false positives, optimal alarm criteria has not been established and it is extremely sensitive to temperature changes [13].

There is growing consensus that multimodal intraoperative monitoring (MIOM) is helpful in spinal surgery because it provides a higher specificity and sensitivity for detecting neurologic injury than any modality used in isolation [14]. EMG, for example, can be combined with SSEPs to improve specificity for motor deficits [13]. However, multimodal intraoperative monitoring is reportedly only available to 65.3% of Canadian surgeons in the operating room [14].

3.4 Current status of research in this area

Several studies have attempted to establish warning criteria for SSEP, MEP, and EMG alerts, but few have used a prospective study design, limiting the range of environmental factors, signal intensities, and spinal deformity conditions included in the evaluation [16, 18-21]. One prospective study of patients who received IONM during spine surgery with SSEPs combined with EMG monitoring, reported the following alerts: 935 were true negative cases, 8 were false negative cases, 66 were true positive cases and 8 were false positive cases, resulting in a sensitivity of 89% and a specificity of 99% [22]. Another study reported sensitivities as low as 13-49% for a range of deficits, contributing to significant debate over the efficacy of MIOM [23]. A prospective case series of 28 pediatric patients who underwent spinal osteotomy with SSEPs combined with and transcranial MEP monitoring recorded information about alerts, corrective actions taken, and success [1]. Increasing blood pressure was the most frequent and effective action taken. Small sample size limited the types of alerts and corrective actions observed, providing insufficient information to establish warning thresholds.

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 maneuvers that can successfully reverse the changes, identify ineffective maneuvers, determine the association between intraoperative factors and incidence of postoperative neurological deficits, or help establish warning criteria.

4 Objectives

4.1 Primary objective

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

4.2 Secondary objectives

- To document intraoperative maneuvers 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 maneuvers
  - unsuccessful maneuvers
- To determine risk factors of intraoperative neuromonitoring alerts
- To make an exploratory analysis of alert patterns and their relation to spinal cord syndromes

4.3 Clinical (biological) hypothesis

There is no formal hypothesis for this study. This study aims to identify both effective and ineffective maneuvers to reverse patient neuromonitoring changes.

5 Study design

This study will be a prospective, interventional, multicenter case series study. There will be no blinding or treatment allocation conducted within this study.

5.1 Study population and patient enrollment

5.1.1 Inclusion criteria

- Age ≥10 years to ≤80 years
- Neurologically intact spinal cord (with or without radiculopathy)
- Undergoing primary or revision procedure in the spine
- Anterior and/or posterior surgical approach for any of the following:
    - Correction of spinal deformity with a major Cobb angle of ≥ 80° in the coronal or sagittal plane
    - Correction of high grade spondylolisthesis (Grades 3- 5)
    - Posterior column or 3-column osteotomy
- Requiring multimodal neuromonitoring with EMG, SSEP, and MEP as per standard of care
- Informed consent obtained for patients i.e.:
    - Ability to understand the content of the patient information
    - Willingness and ability to participate in the clinical investigation according to the Clinical Investigation Plan (CIP)
    - Signed and dated EC/IRB approved written informed consent

    OR
    - Written consent obtained according to defined and IRB/EC approved procedures for patients who are not able to provide independent written informed consent

5.1.2 Exclusion criteria

- Neurodegenerative disease
- Upper motor neuron lesion
- Growing rods or growth guidance procedures
- Tether or staple procedures
- Stand-alone cervical deformity correction procedures
- Any not medically managed severe systemic disease
- Recent history of substance abuse (i.e. recreational drugs, alcohol) that would preclude reliable assessment
- Pregnancy or women planning to conceive within the study period
- Prisoner
- Participation in any other medical device or medicinal product study that could influence the results of the present study

5.1.3 Enrollment of participants

The participating study sites will identify all eligible patients (i.e. all patients who meet all of the inclusion and none of the exclusion criteria). The assessment of eligibility will be performed by the investigator and/or adequately trained member(s) of the research team. The assessment of eligibility includes but is not limited to an inquiry about the interest and willingness of the patient to participate in the research project, a prescreening with questions to confirm eligibility as well as a description of the study and responsibilities for participating. None of the data of the prescreening process will be documented study specifically.

If the patient wishes to participate, a designated member of the research team will go through the informed consent process, which will explain the purpose of the study, the procedures, the risk/benefits, alternatives to participation, and data protection. Each patient choosing to participate will sign and date an ICF. A copy of the signed ICF will be placed into the patient's medical record, the ISF or the patient binder and one copy will be handed over to the patient. A more detailed description of the informed consent process is provided in section 9.

All patients with written informed consent will be allocated to a unique patient trial number. The date of informed consent and the recruitment information is entered in the study database.

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 for reasons specified in section 5.2.5.

For vulnerable patients, special considerations and procedures will be followed as specified in section 9.2.

The recruitment period will be up to 24 months, during which at least 550 patients are planned to be enrolled.

5.2 Study procedures

The schedule of all FU visits as well as the data to be collected at each visit is shown in Table 1.

Table 1: Study schedule

Assessment parameters	Pre- Intra and postoperative visits			
	Visit 1	Visit 2	Visit 3	Visit 4
	Screening/ preoperative	Intraoperative (day 0)	Post-operative (immediately after anesthesia 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 to IONM signal recovery		X		
ASIA LEMS	X		X	X
Sensory function	X		X	X
Spinal cord syndrome			X	X
Neurological deficits *de novo*			X	X
Radiological parameters	X			X**

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

5.2.1 Visit 1: Screening/preoperative visit

- Potential study patients (and their parents/legal guardians in case of a pediatric patients), are informed about the study by the investigator. Before any study-specific examinations are

performed, the patient or legal guardian gives written informed consent to participate in the study according to the CIP. The signed ICF is placed into the patient's medical record, the ISF or the patient binder. The patient receives a copy of the ICF.

- All inclusion and exclusion criteria are checked to decide if the patient can participate in the study.
- All patients that were prescreened for the inclusion and exclusion criteria are entered on the Patient Prescreen and Enrollment Log/Patient Enrollment Log maintained at each study site.
- The baseline characteristics including demographics, medical history, primary diagnosis, diagnosis subtype, pre-operative neurological status (ASIA LEMS sensory function) and radiological parameters will be captured.
- Data verification and entry into the eCRF.

5.2.2 Visit 2: Intraoperative visit (day 0)

- Surgical details such as type of surgery and anesthesia will be collected.
- Intraoperative neuromonitoring alert details will also be captured. For each alert occurring during the procedure, a separate alert form will be completed.
- Information collected will include: IONM Modality, IONM signal at baseline, neuromonitoring alert number, timing of alert, exposure, implant placement, osteotomy/release type, correction, traction, response to alert, Wake up test result, time to recovery of signal in minutes
- Data verification and entry into the eCRF.

5.2.3 Visit 3: Postoperative visit (immediately after anesthesia resolution)

- The neurological examination includes date and time of examination, ASIA LEMS, type of cord syndrome (if present) and sensory function.
- Data verification and entry into the eCRF.

5.2.4 Visit 4: Postoperative visit (Day 30)/discharge (whichever occurs first)

- Neurological examination consisting of ASIA LEMS, presence and type of cord syndrome, and sensory function.
- Radiological parameters will be measured in the first standing radiographic image after surgery.
- Data verification and entry into the eCRF.

5.2.5 Premature study termination

Patient participation in the study may end prematurely for one of the following reasons:

- Patient withdrew informed consent
- Protocol violation
- Sponsor's decision
- Unknown/lost to FU
- Death

For each case of premature termination, the case must be discussed with the sponsor and detailed information will be obtained explaining the circumstances leading to the termination. This will be recorded on a dropout form in the eCRF.

If patients are withdrawn from the study, any collected data will be censored. Censoring allows this collection of data to be accounted for in the analysis.

5.3 Study treatments

All patient treatments are per standard of care based on the discretion of the treating doctor at each participating site.

5.3.1 Study intervention

Study-related interventions are limited to:

- Standardization of the IONM protocol
- Standardization of the threshold for IONM alerts
- Documentation in real time of IONM alerts and maneuvers 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 routine of these patients, but the standardization of the timepoints ensures the proper documentation of the neurological status and comparability.

5.3.2 Postoperative care

Any other postoperative treatment not specifically described in this investigation will be performed according to the standard of care at the study site. There are no specific requirements for the postoperative care related to this study.

6 Definitions of outcome measures and study variables

6.1 Baseline characteristics

6.1.1 Demographics

- Year of birth
- Sex

6.1.2 Medical history

- Height
- Weight
- Type of surgery: Primary or revision surgery
- Blood pressure
- Hemoglobin

6.1.3 Primary diagnosis

The primary diagnoses will be captured as follows: scoliosis, kyphosis, high grade spondylolisthesis, lordosis

6.1.4 Diagnosis subtype

Primary diagnosis subtypes that will be recoded include degenerative, idiopathic, traumatic, congenital, syndromic, neuromuscular

6.2 Surgical details

6.2.1 Surgery

- Date of surgery
- Surgery duration: recorded as time of skin incision and time of skin closure
- Type of surgery
    - Fusion
        - Anterior and/or posterior spinal fusion
        - Levels instrumented in each approach: proximal and distal
        - Levels fused in each approach: proximal and distal
        - Screw placement: free hand, fluoro-assisted, navigation guided, robot guided
    - Decompression
        - Anterior and/or posterior
        - Levels decompressed in each approach
- Interbody devices used, and levels will be recorded as either:
    - Posterior lumbar interbody fusion and/or transforaminal lumbar interbody fusion (PLIF/TLIF)
    - Anterior lumbar interbody fusion and/or oblique lateral interbody fusion (ALIF/OLIF)
    - Direct lateral interbody fusion and/or extreme lateral interbody fusion and/or lateral lumbar interbody fusion (DLIF/XLIF/LLIF)[24, 25]
- Type of osteotomy and levels per osteotomy type:
    - Type 2: posterior column osteotomy (PCO)
    - Types 3 & 4: pedicle subtraction osteotomy (PSO)
    - Type 5 & 6: vertebral column resection (types 5 and 6)
- Intraoperative traction
    - Time of traction application
    - Time of traction removal
    - Cranial traction weight: in kg and as percentage of body weight
    - Caudal traction weight: in kg and as percentage of body weight
- Hemoglobin levels during surgery (if measured): pre-incision, lowest recorded value and final
- Intraoperative transfusions
    - Cell saver (in cc)
    - pRBC (in cc)

6.2.2 Anesthesia

- Total intravenous anesthesia (TIVA): Y/N
- Minimal alveolar concentration (MAC):
    - MAC N_20
    - MAC Halothane Agent
- EEG Depth (Y/N)

6.2.3 IONM

6.2.3.1 Modality

The following details concerning the modality of IONM used will be recorded:

- SSEP monitoring modalities used [26]
    - Tibial (Ptn)
    - Peroneal
    - Ulnar (Uln)
    - Other
- MEP monitoring modalities used [26]:

        - Transcranial
        - Neurogenic motor evoked potentials (NMEP)
        - D Wave: direct spinal cord stimulation inducing a nerve action potential
    - MEP muscle groups and sides used for IONM
        - Rectus femoris (RF)
        - Tibialis anterioris (TA)
        - Abductor hallucis (AH)
        - Abdominal rectus (Abd)
        - Iliopsoas (Psoas)
        - Adductors (Add)
        - Hamstrings (Ham)
        - Medial gastrocnemius (MG)
        - Anal sphincter (Sph)
        - Upper extremity (Upper Ext)
        - Other
    - EMG monitoring modalities used [26]:
        - Free running (Free run)
        - Stimulated (Stim)
        - Pedicle screw stimulation

6.2.3.2 IONM signal at baseline

The IONM signal for SSEP and MEP registered at the start of the surgery will be considered as baseline and will be recorded independently for each side as either:

- Normal
- Absent
- Decreased

Neuromonitoring alerts will be based on changes to this baseline signal

6.3 Primary outcome

6.3.1 Alert criteria

The primary outcome for this study is the incidence of intraoperative neuromonitoring alerts.
A neuromonitoring alert is defined as a major change in neuromonitoring signals such as:

- SSEP: amplitude loss > 50% or
- MEP: amplitude loss > 50% in two of three muscle groups and/or
- EMG: sustained activity for > 10 seconds.

6.3.2 Spinal cord/nerve root monitoring

Ongoing monitoring of the spinal cord is a recurrent process that involves frequent MEP and SSEP trials. MEP trials are run at least every two to three minutes and more frequently during times of high surgical risk and alerts. SSEPs are averaged approximately every five minutes. Nerve roots are monitored continuously by observing free run EMG from the respective muscle groups.

A major SSEP signal change is defined as a greater than 50% loss of amplitude. A major MEP signal change is defined as a greater than 50% loss of amplitude in two of three rectus femoris, tibialis anterior, and abductor hallucis muscles. Amplitude reductions to MEPs and SSEPs are deemed relevant when linked to a specific surgical event, and normal trial-to-trial evoked potentials variability has been excluded. Relevant amplitude changes to MEP and SSEPs should also include decreases in blood pressure and or hematocrit. Technical, anesthetic, and systemic considerations must also be quickly assessed and ruled out.

Significant EMG activity is relevant when linked to a surgical event and sustained for greater than ten seconds. EMG activity arising as a result of the patient being anesthetically light should be excluded.

It is imperative that significant changes to EPs be identified immediately and specific actions be taken based on the type of insult. Management of EP changes include removing or releasing offending instrumentation, increasing perfusion and oxygenation to the cord, open/close osteotomy, and exploring the surgical site for bony fragments that may be compressing the cord. Also, effective management of EP changes can be as simple as application of warm irrigation or ensuing with a brief surgical pause to allow for cord recovery. If no significant improvements are seen, then steroids, although controversial, may be administered. Finally, termination of the surgery must be considered as an option if possible.

A detailed protocol of intraoperative neurophysiological monitoring is provided in Appendix 5.

6.4 Secondary outcomes

6.4.1 Alert details and preceding events

For each alert that occurs during surgery the following details will be recorded:

- Timing of alert
  - Minutes since skin incision
  - Minutes from causative event
- Blood pressure and mean arterial pressure (MAP) at the time of the alert in mmHg
- Hemoglobin at the time of the alert
- Degree of signal loss compared to baseline in SSEP (as percentage) on each side at the time of the alert
- Degree of signal loss compared to baseline in MEP (as percentage) on each side at the time of the alert and muscle group(s) affected
- EMG activity, muscle group affected, duration and activity at closure
- Event preceding an alert (any combination possible)
  - Systemic: eg, low blood pressure, anemia
  - Anesthesia
  - Technical: eg, malpositioned lead, recording interference
  - Surgical cause
    - Exposure
    - Implant
      - Placement: concave, convex, neutral
      - Implant type: screw, hook, wire
      - Implant level
    - Osteotomy/Release
      - Level
      - Osteotomy type: PCO (type 2), PSO (type 3, 4), VCR (type 5,6)
      - Decompression: central, concave side, convex side, posterior body/disc
      - Osteotomy closure
      - Interbody placement
      - Other
    - Correction/Rod placement
    - Traction: pre-incision, pre-implant placement, pre-rod insertion, post rod insertion
    - Other

6.4.2 Intraoperative maneuvers in response to alerts

Maneuvers in response to intraoperative neuromonitoring changes in patients [11] will be recorded as any of the following (including combinations):

Anesthetic	Surgical	Additional measures	Decision
○ Elevation of blood pressure	○ Adjustment of traction	○ Technical	○ Complete case: surgery is completed as intended
○ Blood transfusion (optimize hematocrit)	○ Lessen correction	○ Steroids	○ Case terminated: surgery is ended prematurely
○ Adjustment of anesthesia	○ Rod removal	○ Other	○ Wake up test
	○ Implant removal		
	○ Decompression		
	○ Osteotomy opened		
	○ Osteotomy closed		

- Wake up test: if performed, results from either leg will be recorded separately as either:
  - Normal
  - Weak
  - No movement

6.4.3 Time to IONM signal recovery

- Timing and degree of signal recovery in MEP and SSEP relative to baseline (as percentage)
- Time to recovery of baseline signal in MEP and SSEP or percentage of signal (respective to baseline) at the time of closure. Presence or absence of EMG activity at closure

6.4.4 ASIA lower extremity motor score (LEMS)

The ASIA lower extremity muscle score (LEMS) was derived from manual muscle tests of five lower extremity muscle groups: hip flexor (HF), knee extensors (KE), ankle dorsiflexors (DF), long toe extensor (TE), and ankle plantar flexor (PF) assessed on a scale of strength from 0 to 5 points in which 0 denotes total paralysis and 5 normal active movement against resistance. The motor score provides a means of numerically documenting motor function of the lower extremity. The testing generates two motor grades from L2 to S1 per paired myotome: right and left. A score of 5 for each of the five key muscle functions of the lower extremity would result in a maximum score of 25 for each extremity, totaling 50 for the lower limbs. The motor score cannot be calculated if any required muscle function is not tested [27].

6.4.5 Sensory function

Sensory function is assessed independently for each side starting from the surgical level using the following examinations:

- Light touch: each dermatome is tested using a cotton swab, fingertip or paper napkin. The cheek is touched simultaneously with the same object and the dermatomes are compared to the cheek of the patient who has the eyes closed.
- Pin prick: each dermatome is tested using a needle or sharp object alternating with a dull object. The patient has the eyes closed and is asked to identify if the sensation is dull or sharp.

The results will be recorded as either:

- Normal
- Altered (either decreased/impaired sensation or hypersensitivity)
- Absent

If sensation is altered or absent root level and side affected as well as the lowest normal spine level will be recorded.

6.4.6 Spinal cord syndromes

In incomplete spinal cord injuries there are various degrees of motor function in muscles controlled in levels of the spinal cord caudal to the injury. A number of syndromes have been described based upon the patterns observed after specific areas of the spinal cord have been injured.

6.4.6.1 Anterior Cord

The classic syndrome affects the anterior 2/3 aspects of the cord, which is the watershed supplied by the anterior spinal artery. The zone of perfusion includes the central gray matter, the bases of the bilateral posterior horns, bilateral lateral horns, bilateral anterior horns and the vast majority of the anterior and lateral white matter funiculi. The classic clinical presentation is of loss of motor function (CST and anterior horn) and pain and temperature sensation (SPT) at and below the injury level with sexual dysfunction and loss of urinary and fecal continence (when the thoracolumbar cord is compromised - autonomic / intermediate gray zone injury). There is preservation of the touch, vibration and proprioception senses (sparing of posterior white matter columns). This injury carries the worst prognosis of all of the incomplete spinal cord injuries, with motor recovery in only 39% of patients in the classic syndrome.

6.4.6.2 Central Cord Syndrome

Is the most common acute and incomplete syndrome with damage to the central area of the spinal cord. Patients present with disproportionate upper extremity weakness and less severe lower extremity weakness, sensory and bladder dysfunction.

6.4.6.3 Posterior Cord Syndrome

The classic manifestation includes loss of proprioceptive, tactile and vibratory sensation below the level of the lesion, with preservation of pain and temperature sensation and preserved motor function. Although these patients have motor function and can ambulate, they often have difficulty maintaining balance in the dark or with closed eyes, which is known as a positive Romberg sign (contrary to cerebellar ataxia). The pathophysiology results because the body's sense of positioning (proprioception) requires healthy functioning of the dorsal columns of the spinal cord. Associated weakness and upper motor neuron symptoms, including spasticity and hyperreflexia, can be seen when there is concomitant involvement of the lateral CST - such is the case of subacute combined degeneration secondary to B12 deficiency.

6.4.6.4 Brown-Sequard

Results from a hemisection of the spinal cord. Classic neurological findings include: 1) Ipsilateral flaccid paralysis and total loss of sensation at the dermatomal / myotomal level of the lesion (anterior and posterior horn injury), 2) Ipsilateral spastic paraparesis and loss of proprioception and vibratory sensation below the level of the lesion (lateral CST and posterior white matter columns injury), and 3) Contralateral loss of pain and temperature sensation beginning a few levels below the lesion (SPT injury). Injuries which involve one side of the cord can give “Brown-Sequard like” syndromes.

6.4.6.5 Conus Medullaris Syndrome and Cauda Equina Syndrome

Conus medullaris syndrome and cauda equina syndrome are often mistaken as the same entity. By definition, in conus medullaris syndrome (CMS), the injury involves the cord at the level of L1 or L2. In contrast, in cauda equina syndrome (CES), the injury only involves the nerve roots of the cauda equina and spares the spinal cord itself. In CMS, usually, there is early sensory deficit (saddle distribution) and bladder and bowel dysfunction. The motor symptoms are mild (symmetric mixed UMN and LMN syndrome with both spasticity and flaccid paresis/paralysis, hyperreflexia and hyporeflexia). On the other hand, in CES, there is early and more conspicuous motor symptoms (asymmetric lower motor neuron syndrome with flaccid paresis/paralysis and areflexia) as well as asymmetric radicular pain. In CES there is bladder and bowel dysfunction later in the course as compared with CMS.

6.5 *De novo* neurological deficits

A neurological deficit *de novo* is defined as any of the following:

- postoperative decrease of one point from baseline in the ASIA LEMS
- worsening in sensory function from baseline
- presence of spinal cord syndrome

6.6 Radiological parameters

- Maximum coronal Cobb angle: measures coronal thoracic kyphosis in degrees [28]
- Maximum sagittal Cobb angle: measures sagittal thoracic kyphosis in degrees [28]
- Coronal apex: most translated vertebra of a scoliotic or kyphotic curve in the coronal plane.
- Sagittal apex: most translated vertebra of a scoliotic or kyphotic curve in the sagittal plane.
- Coronal deformity angular ratio (DAR): maximum Cobb measurement in the coronal plane divided by number of vertebrae involved expressed in degrees per level [29]
- Sagittal deformity angular ratio (DAR): maximum Cobb measurement in the sagittal plane divided by number of vertebrae involved expressed in degrees per level [29]
- Coronal C7 plumb line (PL): measures coronal balance in millimeters distance between C7 plumb line and central sacral vertical line [30]
- Sagittal C7 plumb line (PL): measures sagittal balance in millimeters distance between C7 plumb line and central sacral vertical line [30]

7 Statistical planning

7.1 Hypotheses

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.

7.2 Sample size considerations

7.2.1 Sample size estimation

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 follow-up. 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 intraoperative neuromonitoring 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.

7.3 Statistical analysis

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. Incidence of alerts will be presented as frequencies and percentages of occurrence and as total number of alerts per patient. Significance will be defined as $p<0.05$.

A detailed Statistical Analysis Plan (SAP) will be prepared for this study before the final analysis. An overview is presented in the following sections.

7.3.1 Analysis populations

The full analysis population includes all patients who provided a signed informed consent and commenced treatment within the study ("enrolled" patients). This population will be used for the analysis of both primary and secondary objectives.

The per-protocol population is a subset of the full analysis population, which excludes patients with protocol deviations which are relevant for the primary analysis (as defined during the data review meeting prior to final analysis). Per protocol analyses will also be conducted as a sensitivity analysis of the full analysis population analysis, if applicable.

7.3.2 Protocol deviations

Protocol deviations may include but are not limited to issues relating to eligibility, consent, and dropout from FU, punctuality during visits. All protocol deviations are reviewed during the data review meeting prior to final analysis.

7.3.3 Patient discontinuation

Enrolled patients who withdraw from study FU for any reason (withdrawal of consent, death, loss to FU, etc.) will be included in the analysis until the time at which they dropped out.

7.3.4 Missing data

Some degree of missing data is expected for both baseline characteristics and outcomes for this study. Patients may withdraw from the study prior to completion of the FU period for reasons such as death, severe intercurrent illness, withdrawal of consent, and loss to FU. In general, missing data due to study withdrawal will be considered to be non-informative. For each endpoint, a decision will be made as to whether special methods of analysis need to be employed to handle missing data on an endpoint-by-endpoint basis, and this will be documented prior to the final analysis. The decision will be based upon the extent of missing data, the likelihood of bias occurring as a result of missing data, and the importance of each endpoint.

7.3.5 Efficacy analyses

Primary analysis

The primary analysis for this study will consist of descriptive statistics pertaining to the incidence of intraoperative neuromonitoring alerts. These results will be presented as a frequency and percentage of events that occurred within the study population.

Secondary analyses

Secondary analyses will be completed to provide descriptive statistics regarding the following variables:

- Number of alerts (reported as frequency and percentage and as total number per patient)
- Degree of change in the monitoring signals (SSEP and MEP) (reported as frequency and percentage of patients with 100% loss, >75% loss, >50% loss, and no loss for both the right and left side)
- Degree of change in EMG (reported as frequency and percentage of EMG activity occurrence, as well as the duration of activity reported as mean and standard deviation).
- Event preceding an alert (reported as frequency and percentage)
- Timing of alert (reported as mean and standard deviation in minutes from causative event)
- Sensitivity and specificity of the alerts to detect neurological deficits using a minimum threshold of 50% change in the signal (reported as a percentage specificity and sensitivity)

Additionally, the success rate of reversal maneuvers to restore signal beyond the threshold of 50% change will be assessed as frequencies and percentages:

- Number and type of maneuver in response to an alert
  - Number and type of successful maneuvers
  - Number and type of unsuccessful maneuvers
  - Timing to restoration of any signal (reported as categories) and analyzed using different approaches to deal with this variable using lower limit, mean and upper limit of the time interval
  - Timing to restoration of baseline signal (reported as categories) and analyzed using different approaches to deal with this variable using lower limit, mean and upper limit of the time interval

Patient neurological status at follow-up/discharge will also be analysed using the following measures:

- LEMS (reported as mean and standard deviation derived as sum of 5 muscle points each side)
- Deficits *de novo* (reported as frequency and percentages) in motor function, sensory function and newly developed cord syndromes

Association between neurological deficit and intra-operative alerts (on patient level) will be evaluated using the chi-squared test.

Potential predictors of neuromonitoring alerts will be assessed using logistic regression analysis. Selection of the study parameters to enter in the final multivariable prognostic model will be done according to a first univariable analysis and/or principal component analysis. Based on Cohen's approach (10 events needed for each potential predictor), this study would require 100 patients experiencing intraoperative neuromonitoring changes to include 10 predictors in the model [31].

8 Risk Analysis

8.1 Patient risk analysis

The risks that occur in this study are mainly associated with the general risks of surgery for spinal deformity. As the study intervention concerns the standardization of the IONM, alert threshold and neurological assessments, study-related risks are considered minimal.

8.1.1 Study-related risks

The main risk associated with the participation in the study is loss of privacy. Patients' private and confidential medical information may get disclosed and confidentiality broken. See section 8.1.2 for measures how to minimize such risks.

The study-related intervention is not expected to result in additional risks for participating patients. All patients will be treated as per standard of care of the hospital.

8.1.2 Actions to minimize increased patients risks

General treatment-related risks will be present whether the patient participates in the study or not. Such risks will be managed by use of standards of treatment at the participating study sites. The risk of loss of privacy and confidentiality will be managed by strict adherence to data safety and security procedures explained elsewhere in this CIP and in the applicable sponsor's SOPs.

The study will be implemented according to current valid international guidelines (ICH-GCP and ISO 14155). The ethical position is based on the Declaration of Helsinki, thus guaranteeing optimal protection of patient interests.

9 Informed consent process

9.1 General process for obtaining informed consent

Whenever possible, consent will be obtained from every patient before any study-specific procedures or assessments take place. The written patient information/ICF will explain benefits, risks, study procedures and study aims using a plain, understandable language. It will be explained to the patient that he/she is free to enrol in the study and withdraw at any point without prejudice regarding the future treatment. The patient will signify his/her willingness to participate in the study by signing and dating a personal copy of the approved ICF. The investigator will keep the original ICF in the ISF and provide the patient with a copy.

9.2 Special considerations to consent vulnerable patients

In this study, vulnerable patients may be included for the following reasons:

- Patients in an emergency situation
- Mentally incompetent patients (temporarily or permanently)
- Patients able to give oral consent only

- Pediatric patients

The procedures of including vulnerable patients from the above categories are specified in section 9.2.1.

9.2.1 Mentally incompetent patients and emergency treatments

According to the ISO 14155 guideline (ISO section 4.7.3.2), when a patient is unable to make the decision to participate in a clinical investigation prior to surgery, the patient may still be enrolled according to the surrogate consent process described below.

More specifically, for patients who are eligible for this study and undergo emergency treatments, prior informed consent of the patient may not be possible due to the patient's medical condition. In case of such emergency situations a procedure for obtaining surrogate consent will be suggested to the local ECs according to the ISO 14155 guideline (ISO section 4.7.3.4):

Surrogate consent

- Surrogate consent will be obtained according to local regulations (eg from the PI, an independent medical person, the patient's relatives, legal representative etc). Each clinic will be instructed about the local regulations and guidelines in a separate document.
- Arrangements are made to inform the patient (or legally authorized representative) as soon as possible about the patient's study participation and all aspects of the study.
- The patient is asked to provide informed consent for continued participation as soon as his/her medical condition allows.
- If the patient disagrees to participate in the clinical investigation, the PI makes sure that no data of this patient is collected. No more study-specific interventions will be performed unless treatments necessary to assure the patient's safety.
- If the patient remains mentally incompetent during the whole period of study participation, the patient's legally authorized representative is approached who is informed about all aspects of the study as well as the patient's rights. The legal representative is asked to give informed consent. If the legal representative disagrees that the patient participates in the study, the PI makes sure that no data of this patient is collected. No more study-specific interventions will be performed unless treatments necessary to assure the patient's safety.

9.2.2 Patients able to give oral consent only

If the patient is unable to give written informed consent by signing the ICF due to medical reasons (eg neurological impairment), the following procedures will be performed:

- The investigator orally informs the patient about the study.
- The patient decides about study participation and provides oral consent to participate in the study.
- A witness confirms the patient’s oral consent by signing the ICF.
- If the neurological impairment is only temporarily present, the consent to remain in the study will be obtained from the patient as soon as he/she is able to sign the ICF.
- If the neurological impairment is present during the whole study period, the patient's legal representative will sign the ICF as soon as possible to confirm the patient's agreement to remain in the study.

9.2.3 Special considerations to consent pediatric patients

In case of pediatric patients, the parent(s) or legal guardian(s) are informed about the study and provide informed consent using a specific information and informed consent form. For the children, patient information sheets are provided containing information where the content and wording are adapted for the age group(s) of involved children. In any case, the child is informed orally in an adequate way. Written informed consent needs to be obtained from the parent(s) or legal guardian(s). Assent is obtained from any child considered to be able to understand the basic information provided. A member of the research team will go through the informed consent process, discussing screening questions to confirm eligibility as well as a description of the study including the purpose, procedures, risk / benefits, alternatives to participation, data protection and the responsibilities for participating. It will be explained to the patient and parent/legal guardian that he/she is free to participate in the study and withdraw at any point without prejudice regarding future treatment.

The investigator will keep the original Informed Consent in the ISF and provide the patient with an official copy.

10 Adverse event reporting

In this clinical investigation, and based on the risk analyses, AEs or serious AEs (SAEs) according to ISO 14155 will not be collected. Only neurological complications are collected as one of the main outcomes of this investigation.

11 Data management

11.1 Data collection, source data, storage and archiving

Data management will be performed by AOCID. Data handling and protection is conducted according to the ISO 14155 guidelines and ICH-GCP and applicable regulations.

A study-specific Data Management Plan describes all details of data management and quality control of the SDIM database at AOCID. The CRF collects data from each participating site. Specifically, all data on each patient participating in the study are documented in the CRF. The CRF contains data items as specified in this CIP. Modification of the CRF will be made only if deemed necessary and in accordance with any amendment to the CIP.

11.1.1 Electronic CRF

For this study, an eCRF is designed to accommodate the specific features of the study design. The electronic data capture system software solution used for this registry is REDCap (Research Electronic Data Capture). REDCap is a browser-based, metadata-driven EDC software solution and workflow methodology for building and managing online databases developed by the Vanderbilt University.

Access to the eCRF is password protected and specific functions are assigned (eg SC, investigator, CRA, etc). The eCRF is to be completed in a timely manner after a patient's visit (ie 14 days after occurrence of a documentable event).

After termination of the study, each study site will receive an electronic copy of the data collected at the respective study site.

11.1.2 Source data

Generally, data collected in the hospital patient charts are considered source data. In order to facilitate data collection at study sites, a set of data worksheets will be provided. On these worksheets, additional data may be collected that is not routinely documented in the hospital patient chart. For such additional data, the worksheet is considered to be the source document and has to be kept at the study site accordingly. Additional data that is not routinely documented in the hospital patient chart may be collected in the CRF only. For such additional data, the CRF is considered to be the source document. Data collected on patient and surgeon questionnaires are also regarded as source data.

Source data and any other essential documents have to be archived according to legal requirements at the study site. Clinical study data CRF (ie eCRF and if available, original paper CRF) and essential documents are to be archived by the sponsor according to legal requirements. In case there are no contradictory laws, the minimum archiving required by AOCID is 10 years after the Final Study Report (FSR) was finalized.

11.2 Confidentiality

Privacy and confidentiality of the patient's medical data will be maintained through the study. eCRF and all other documents sent to the sponsor will be identified only with the numeric patient's identifier code. The study site will maintain the link between the patient identifier code and the patient's names.

Fully identifiable information may be reviewed for the purpose of verifying data in the eCRF only at the location of the study site. This can be carried out by the sponsor or sponsor’s designee, regulatory agencies or quality assurance personnel. Study site-specific regulations and procedures may apply and will be followed by the above listed personnel. Personal medical information will be treated as confidential at all times. The informed consent document will contain information about the confidentiality of the medical information and approval for the access.

12 Study management and quality control

12.1 Contract Research Organization

No contract research organization (CRO) is contracted to perform this clinical investigation.

The sponsor delegates specific tasks and responsibilities to AOCID. AOCID acts as a CRO in this clinical investigation. The delegation of all tasks and responsibilities is regulated in a specific agreement between the sponsor and the CRO.

12.2 Training and organization at the study site

Prior to recruiting the first patient, the study site PI(s), Sub-Investigators (SI), and SC(s) will undergo a defined training program. This will occur during the site initiation visit. The training includes explanations of the CIP procedures, inclusion and exclusion criteria, the CRF and general aspects of ISO 14155 and GCP. The training will be performed by AOCID. A training record is maintained for all study site personnel involved in study-specific activities. In the case of a change in the study site personnel, the new staff has to undergo the same training program. All research team members need to have current GCP or equivalent training/certification.

The SC with primary responsibility for managing the study at each study site will be provided with comprehensive training on the study procedures, CIP, duties and responsibilities of the SC. An ISF will be provided to each study site for holding all essential documents and training documentation. The PI at each study site will be responsible for the supervision of the study and will provide direction and training to all other research personnel, as necessary.

12.3 Study monitoring

Designated and adequately trained AOCID personnel (ie CRA) will perform on-site monitoring visits (MV) as frequently as required. At these visits, the CRA will compare the data entered into the CRF with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to AOCID and study site personnel and are accessible for verification by the AOCID CRA.

Direct access to source documentation must be allowed for the purpose of verifying that the data in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the study site personnel. AOCID expects that during monitoring visits, the relevant research team members will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The CRA will meet with the PI on a regular basis during the study to provide feedback on the study conduct.

13 Data safety monitoring board/safety officer

No DSMB/Safety officer (SO) was implemented for this study.

14 Regulatory affairs

The CIP, associated documents, investigator's financial disclosure, the patient information and ICFs will be sent to a respective EC/IRB for evaluation and approval. The relevant EC/IRB will be kept informed about the study progress and events according to their specific regulations and procedures.

If regulatory approvals are necessary in participating study sites, the study will commence in those places only after final approvals have been granted by the appropriate authorities. If required, the individual study site will have to submit the documents to any local review board as defined by the local hospital policy.

15 Patient insurance

The Sponsor ensures insurance coverage of liability in clinical trials for all patients participating in this clinical study. General liability insurance is always valid and in full force.

16 Study report and publication policy

16.1 Final Study Report

The results of the statistical evaluation will be summarized in a report, which forms the basis for the comprehensive FSR. The comprehensive FSR forms the basis for all future publications. AOCID will be in charge of writing the FSR. The PCI will review and comment on the FSR.

16.2 Publication

The publication strategy will be decided between the sponsor, PCI, AOCID, and any other affected party. A publication strategy will be agreed upon and is available as a separate agreement.

17 Termination criteria

The progress of the study, in particular the enrollment and safety aspects, will be closely monitored together with the sponsor. The sponsor may decide to terminate the study for reasons as defined in section 17.1. In case of an early study termination, all patients already enrolled in the study will be followed up until the last FU visit as defined in the CIP.

17.1 Stopping rules

There will not be stopping rules implemented during the course of this study as there is no specific study treatment. All procedures will be conducted as usual standard of care within the study sites, which will remain unaltered by this study.

18 Deviations from the Clinical Investigation Plan

Deviations from the procedures as described in this CIP or altering the CIP without following a defined process are not permitted. Should deviations from the protocol occur, AOCID must be informed in an expedited manner, depending on the seriousness of the deviation.

A CIP deviation is any non-adherence to the protocol that does not involve the inclusion/exclusion criteria, primary efficacy variable, and GCP guidelines. CIP deviations are minor and do not impact the study in a major way. CIP deviations are to be reported to the sponsor within ten working days.

A CIP violation is any significant divergence from the protocol on the part of the patient, investigator, AOCID, sponsor, or any other responsible party that affects eg the inclusion/exclusion criteria, primary efficacy variable, or GCP guidelines. AOCID must be notified within five working days of the occurrence. Violations will be recorded at the study site and in the CRF.

Corrective measures are taken depending on the significance and seriousness of the CIP deviation. Such measures may be reminding the PI about his/her obligations, re-training personnel at the study site or, in serious cases, the closure of the study site and respective reporting to the EC/IRB. Serious cases of CIP deviations include cases as listed above. Repeated violations may lead to closure of the study site.

19 Amendments to the Clinical Investigation Plan

No changes to the approved CIP are allowed, except when the change removes immediate threats for the patient safety or is of a purely administrative or logistic nature. Any change to the CIP made to protect the life and well-being of the enrolled patients must be reported to AOCID within five days.

Should there be any need during the performance of the study to change this CIP, an amendment will be developed, issued and approved by or notified to the required bodies as described in the AOCID internal procedures.

20 Time schedule

First ethical submission			Dec 2018/Jan 2019
Ethics Committee approvals	April 2019	to	Nov 2019
First patient/first visit			May 2019 (estimated)
Last patient/first visit			Aug 2021 (estimated)
Last patient/last visit			Sep 2021 (estimated)
Data cleaning and analysis	Sep 2021	to	Nov 2021 (estimated)
Final Study Report	Nov 2021	to	Feb 2022 (estimated)

21 Quality assurance

AOCID's quality assurance policies and guidelines apply to the planning, selection of investigators and participating study sites, contracts, monitoring, recording of data and its analysis, documentation and archiving, evaluations, and reporting of the entire clinical investigation. The AOCID quality management system is based on the principles of ISO 9001, ISO 14155 and ICH E6 Guideline.

22 Authors

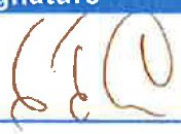
CIP developed by:

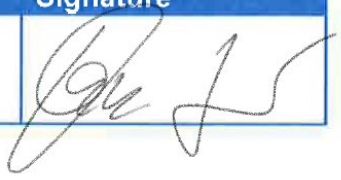
Dr. Stephen J. Lewis, MD, MSc, FRCS(C)	University Health Network
Anahi Hurtado	Senior Project Manager Medical Affairs AOCID
Christian Knoll	Project Manager Medical Statistics AOCID
Dr. Lawrence Lenke, MD	Co-Principal Coordinating Investigator/Regional Principal Coordinating Investigator

CIP reviewed by:

Brigitte Gallo	Head Clinical Operations AOCID
Yabin Wu	Research Project Manager AOSpine
Niccole Germscheid	Global Research Manager AOSpine
Alexander Joeris	Head Medical Affairs AOCID
Martin Schuler	Director AOCID

CIP approval signatures

Name	Function	Date	Signature
Dr. Stephen J. Lewis, MD, MSc, FRCS(C)	Principal Coordinating Investigator	Dec 15, 2018	

Name	Function	Date	Signature
Martin Schuler	Director AOCID	17.12.2018	

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24 Appendix 1 Signature of Principal Investigators from each study site

Study site _____

CIP approval signature of Principal Investigator

Name	Position	Date	Signature

With signing this statement, I agree and confirm:

- To have read and understood this CIP and to have informed and to have supervised the appropriate training of all research team members of this study site involved with the conduct of the study.
- To assume responsibility to conduct the study in compliance with this protocol and future amendments at this study site.
- To obtain written approval from the IRB or the independent EC before initiating the clinical investigation at this study site.
- To not implement any changes to the protocol or the corresponding procedures without written agreement from the sponsor and the EC/IRB, except where necessary to eliminate immediate risk to the study patients.
- That I and all team members involved in the conduct of this clinical investigation are aware and trained in all relevant aspects of the ICH E6 (GCP) Guideline and all applicable regulatory requirements.

25 Appendix 2: SDIM: Baseline, Intra-Op and Post-Op Datasheet

AOSPINE

Patient identifier: _____ Surgery date ____/____/_____
MMM/ DD / YYYY

SDIM Baseline, Intra-Op and Post-Op Datasheet

DEMOGRAPHICS

DOB ____/____/_____ ☐ Male ☐ Female Height_____cm Weight _____kg

☐Primary ☐Revision Baseline Pre-op BP _____/_____mmHg Baseline Pre-Op Hemoglobin _____

Primary Diagnosis: ☐Scoliosis ☐Kyphosis ☐High Grade Spondylolisthesis ☐Lordosis

Subtype: ☐ Degenerative ☐ Idiopathic ☐ Traumatic ☐ Congenital ☐ Syndromic ☐ Neuromuscular

Max Coronal Cobb _____° Apex_____ Cor DAR _____°/level Coronal C7 PL _____ (mm)

Max Sagittal Cobb _____° Apex_____ Sag DAR _____°/level Sagittal C7 PL _____ (mm)

CASE

Time of Skin Incision _____ Time Skin Closed _____

	Levels Instrumented		Levels Fused	
☐ **Anterior Spinal Fusion**	Proximal_____	Distal_____	Proximal_____	Distal_____
☐ **Posterior Spinal Fusion**	Proximal_____	Distal_____	Proximal_____	Distal_____

Screw placement ☐ Free hand ☐ Fluoro-assisted ☐ Navigation guided ☐ Robot guided

☐ **Anterior Decompresion** Levels _____

☐ **Posterior Decompresion** Levels _____

☐ **Interbody devices** ☐ No ☐ Yes (If yes, please complete)

- ☐ PLIF/TLIF Levels_____
- ☐ ALIF/OLIF Levels_____
- ☐ DLIF/XLIF/LLIF Levels_____

Osteotomy: ☐ No ☐ Yes (If yes, please complete)

☐ Posterior Column Osteotomy (Type 2) Levels:_____

☐ Pedicle Subtraction Osteotomy (Type 3,4) Levels:_____

☐ Vertebral Column Resection (Type 5,6) Levels:_____

Intra-Operative Traction ☐ No ☐ Yes (If yes, please complete)

Time of Traction Application_____ Time of Traction Removal _____

Traction Weight (cranial) _____ kg (_____% BW) Traction Weight (caudal) _____ kg (_____% BW)

Intra-Operative Hemoglobin measured (g/dl) ☐ No ☐ Yes (If yes, please complete)

Pre-incision Intra-op_____ Lowest Recorded Intra-op _____ Final Recorded Intra-op _____

Intra-Operative Transfusions Given ☐Yes ☐No If Yes: Cell Saver _____cc pRBC _____cc

First Radiographic Outcome after Surgery Date ___/_____/___

Max Coronal Cobb _____° Apex_____ Cor DAR _____°/level Coronal C7 PL _____ (mm)

Max Sagittal Cobb _____° Apex_____ Sag DAR _____°/level Sagittal C7 PL _____ (mm)

Appendix 2_Baseline, Intra-and Post-OP datasheet_v1.1

AOSPINE

Patient identifier: _____ Surgery date____/____/_____
MMM/ DD / YYYY

Pre-Operative Neuromonitoring and Neurological Examination Data Form

PREOPERATIVE NEUROLOGICAL ASSESSMENT

Lower Extremity Motor Score- ASIA LEMS (___/5)

LEFT HF _____ KE _____ DF _____ PF _____ TE _____

RIGHT HF _____ KE _____ DF _____ PF _____ TE _____

(HF: hip flexion; KE: knee extension; DF: ankle dorsiflexion; PF: ankle plantar flexion; TE: great toe extension)

Sensory Function (from the surgical level)

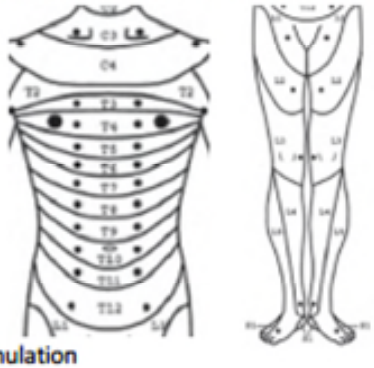
LEFT light touch: ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level_____

RIGHT light touch: ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level_____

LEFT pin prick: ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level _____

RIGHT pin prick: ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level _____

Root Sensory Abnormality: Level(s) & side(s) involved_____



MONITORING MODALITIES USED (Tick all that apply)

☐ **SSEP** ☐ Ptn ☐ Peroneal ☐ Uln ☐ Other

☐ **MEP** ☐ Transcranial ☐ NMEP ☐ D Wave

☐ **EMG** ☐ Free run ☐ Direct nerve Stimulation ☐ Pedicle screw Stimulation

MEP Muscle Groups Used:

LEFT: ☐ Abd ☐ Psoas ☐ Add ☐ RF ☐ TA☐ AH ☐ Ham ☐ MG ☐ Upper Ext ☐ Sph ☐ Other_____

RIGHT: ☐ Abd ☐ Psoas ☐ Add ☐ RF ☐ TA☐ AH ☐ Ham ☐ MG ☐ Upper Ext ☐ Sph ☐ Other_____

ANESTHESIA:

TIVA ☐Yes ☐No If No: MAC N_2O_____ MAC Hal Agent_____ EEG Depth ☐Yes ☐No

NEUROMONITORING SIGNAL AT BASELINE:

LEFT MEP: ☐Normal ☐Absent ☐Decreased **LEFT SSEP:** ☐Normal ☐Absent ☐Decreased

RIGHT MEP: ☐Normal ☐Absent ☐Decreased **RIGHT SSEP:** ☐Normal ☐Absent ☐Decreased

---

Significant Monitoring Alert? (MEP, SSEP: amplitude loss >50%, EMG: sustained activity)

☐YES ☐NO If Yes, please complete a **SDIM Intra-Operative Alert Form** for **EACH** independent alert

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Appendix 2_Baseline, Intra-and Post-OP datasheet_v1.1

Appendix 3: SDIM: Intra-Operative Alert Form

AOSPINE

Patient identifier: _____ Surgery date____/____/_____
MMM/ DD / YYYY

SDIM Intra-Operative Alert Form

NEUROMONITORING ALERT # _____

Time of Alert_____min (from skin incision) **Time of Alert**_____min (from causative event) ☐Unknown
BP at time of alert _____/_____**mmHg** **MAP** _____**mmHg** **Hemoglobin** at time of alert ____ ☐Unknown
EMG Activity: ☐YES ☐NO Muscle Group(s) _____ Duration _____min **Activity at Closure** ☐YES ☐NO

Group(s) Affected (MEP)
LEFT: ☐ Abd ☐ Psoas ☐ Add ☐ RF ☐ TA ☐ AH ☐ Ham ☐ MG ☐ Upper Ext ☐ Sph ☐ Other____
RIGHT: ☐ Abd ☐ Psoas ☐ Add ☐ RF ☐ TA ☐ AH ☐ Ham ☐ MG ☐ Upper Ext ☐ Sph ☐ Other____

Event preceding the Alert: ☐ Systemic ☐ Anesthesia ☐ Technical ☐ Surgical cause
☐ **Exposure**
☐ **Implant Placement** ☐Concave ☐Convex ☐Neutral **Implant Type** ☐Screw ☐Hook ☐Wire Level____
☐ **Osteotomy/Release** Level_____
Osteotomy Type: ☐ PCO (Type 2) ☐ PSO (Type 3,4) ☐ VCR (Type 5,6)
☐ Decompression ☐ Central ☐ Concave side ☐ Convex side ☐ Posterior body/disc
☐ Osteotomy Closure
☐ Interbody Placement
☐ Other _____
☐ **Correction/ Rod Placement**
☐ **Traction** ☐ Pre-incision ☐ Pre-implant placement ☐ Pre-Rod insertion ☐ Post Rod insertion
☐ **Other** _____

Response to Alert (tick all that apply) ☐ Elevate BP ☐ Give Blood ☐ Adjust Anesthesia ☐ Technical
☐ Rod Removal ☐ Implant Removal ☐ Osteotomy Opened ☐ Osteotomy Closed ☐ Adjust Traction
☐ Steroids ☐ Decompression ☐ Lessen Correction ☐ Complete case ☐ Case Terminated ☐Other_____

Wake up Test: ☐YES ☐NO If Yes (results):
Left Leg ☐ Normal ☐ Weak ☐ NO movement **Right Leg** ☐ Normal ☐ Weak ☐ NO movement



Time to Recovery of Signal
Comments:_____
_____
_____
_____

Appendix 3- SDIM: Intra-OP Alert Form_v1.1

26 Appendix 4: SDIM: Neurological assessment

AOSPINE

Patient identifier: _____ Surgery date____/____/_____
MMM/ DD / YYYY

SDIM: Neurological Assessment

FIRST POST-OPERATIVE NEUROLOGICAL ASSESSMENT (First Recordable Physical Exam after Reversal of Anesthesia)

Date of examination_____ Time_____

Lower Extremity Motor Score- ASIA LEMS (___/5)

RIGHT	HF _____	KE _____	DF _____	PF _____	TE _____
LEFT	HF _____	KE _____	DF _____	PF _____	TE _____

(HF: hip flexion; KE: knee extension; DF: ankle dorsiflexion; PF: ankle plantar flexion; TE: great toe extension)

Sensory function below the surgical level

Right: Light touch ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level_____

Left: Light touch ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level_____

Right: Pin prick ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level_____

Left: Pin prick ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level_____

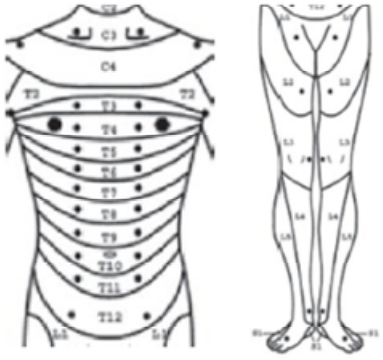
Root: Level(s) & side(s) involved _____

Spinal Cord Syndrome ☐ No ☐ Yes, If Yes, choose from below

☐ Complete

☐ Incomplete

- o Anterior Cord
- o Central Cord
- o Posterior Cord
- o Brown-Sequard



DISCHARGE NEUROLOGICAL ASSESSMENT

Post-op Day_____ (Date of discharge or maximum 30 days post-op)

Lower Extremity Motor Score- ASIA LEMS (___/5)

RIGHT	HF _____	KE _____	DF _____	PF _____	TE _____
LEFT	HF _____	KE _____	DF _____	PF _____	TE _____

(HF: hip flexion; KE: knee extension; DF: ankle dorsiflexion; PF: ankle plantar flexion; TE: great toe extension)

Sensory function below the surgical level

Right: Light touch ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level_____

Left: Light touch ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level_____

Right: Pin prick ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level_____

Left: Pin prick ☐ Normal ☐ Altered ☐ Absent If altered or absent, lowest normal level_____

Root: Level(s) & side(s) involved _____

Spinal Cord Syndrome ☐ No ☐ Yes, If Yes, choose from below

☐ Complete

☐ Incomplete

- o Anterior Cord
- o Central Cord
- o Posterior Cord
- o Brown-Sequard

Appendix 4-SDIM: Neurological Assessment Form_v1.0

27 Appendix 5: Intraoperative neurophysiological monitoring protocol

Intraoperative neurophysiological monitoring protocol

Anesthesia

The use of a total intravenous anesthetic is the optimal choice for monitoring purposes. The most common combination of intravenous agents are opioids and propofol, in conjunction with a benzodiazepine. The use of muscle relaxants, halogenated agents, and nitrous oxide are avoided completely or used sparingly for induction only. Maintenance of anesthesia is with a mixture of 30% oxygen in air, continuous infusion of propofol at a rate of 100–200 µg/kg/min, and continuous infusion of remifentanil (or narcotic of choice) adjusted according to hemodynamic response. Infusions are discontinued after surgery.

Strict regulation of hematocrit levels and blood pressure should be monitored, and deliberate hypertension may be induced when stressing the spinal cord such as during deformity reduction.

Level of Consciousness, EEG and the BIS Monitor

The accumulation of propofol in body tissue can cause anesthetic deepening and result in amplitude changes in evoked potential (EP) signals. This phenomenon is referred to as anesthetic fade and can be avoided with the use of a Bispectral Index Monitor (BIS), or electroencephalography (EEG) recordings. Infusion rates can be adjusted accordingly to maintain an approximate BIS value of 45-55. A compressed spectral array (CSA) can be used to maintain an EEG power ratio of approximately 50% 1-7 Hz (delta and theta) and 50% 8-15 Hz (alpha and beta). Maintaining consistent levels of anesthesia will also facilitate a prompt emergence if necessary.

Baselines

Baseline motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP) are obtained after anesthetic induction and prior to incision or application of skull-femoral traction. Post-induction baselines serve to avoid any drug related suppression of signals that may occur with induction. A minimum of 3 consecutive should be obtained to confirm stability of responses. For cases that involve unstable spines, baselines are obtained in supine position, and the use of volatile agents and muscle relaxants are avoided altogether. This enables monitoring of the spinal cord throughout the entire stage of positioning.

Motor evoked potentials

MEPs are elicited using transcranial electric stimulation. Alternating anodal stimulation is delivered between two electrodes placed 2 cm anterior to C1–C2 (international 10–20 system) overlying the motor cortex region. Trains of four to nine pulses, spaced at an interstimulus interval ranging from 1.1 to 4.1 ms, are delivered with constant voltage (200–600 V) at the anode. Stimulation parameters are optimized to achieve maximal amplitude for the individual patient.

Resultant compound muscle action potentials (CMAPs) are recorded using a bipolar montage for each group. Muscle groups are selected based on the type of surgery, level of surgery, and nerve root involvement, if any. All myogenic responses are recorded bilaterally. Procedures above the conus must include rectus femoris, tibialis anterior, and abductor hallucis muscles. Extra groups can be used, if deemed necessary, such as abdominal rectus, iliopsoas, adductors, hamstrings, medial gastrocnemius, and anal sphincter muscles.

At least one upper extremity muscle group is monitored to act as a control. Unaveraged compound muscle action potentials are recorded through a 30–1,500-Hz bandpass filter and are displayed in a 100-ms window.

Somatosensory evoked potentials

Cortical and subcortical somatosensory evoked potentials are recorded after stimulation of the left and right posterior tibial nerves and is delivered through electrodes placed over the posterior tibial nerve at the medial malleolus. Peroneal nerve SSEPs should be recorded for cases that involve risk to the L5 nerve roots such as reduction of spondylolisthesis. Stimulation for the peroneal nerves is delivered through electrodes placed at the ankle between the extensor hallucis longus and extensor digitorum longus tendons. Ulnar and/or median nerve SSEPs are recorded for use as controls. Ulnar nerve SSEPs are preferred as they can be used to monitor positional injuries.

All SSEPs are elicited by a constant current 300-µs square-wave pulse delivered at a rate of 4.7 per second. Stimulation intensity levels typically range from 15 to 40 mA, with the selection of intensity based on maximal amplitude response for the individual patient. Signals are averaged until a clear, reproducible waveform can be identified. Cortical potentials are recorded from subdermal needle electrodes placed at Cpz, Cp3, and Cp4 and are referenced to Fpz according to the international 10–20 system using a bipolar montage. In addition, posterior tibial nerve cortical potentials are also recorded using a transverse montage. Subcortical potentials are recorded similarly with an electrode placed over the region of the second cervical vertebra referenced to Fpz. Responses are recorded through a 30–500-Hz bandpass filter, and waveforms are displayed in a 50-ms window for ulnar nerve and 100-ms window for posterior tibial nerve.

Free Run Electromyography

Free run EMG is recorded from muscle groups selected based on nerve root involvement recorded through a 30–1,500-Hz bandpass filter.

Positional Safety Check

Once the spinal cord is deemed to be safe and all EP signals remain reproducible and stable, the patient is observed for any impending peripheral nerve injuries due to the positioning itself. If the patient is prone, ulnar nerve SSEPs and first dorsal interosseous MEPs are utilized for detection of brachial plexus compression and/or ulnar nerve compression or stretch. The park bench or lateral decubitus position places the downward ulnar nerve, brachial plexus, and peroneal nerve at the fibular head at risk. The peroneal nerve can be assessed by monitoring tibialis anterior MEPs or by eliciting peroneal nerve SSEPs by stimulating below the fibular head. Improper intraoperative positioning can result in significant peripheral nerve injuries, so rigorous preventative measures should be undertaken to eliminate as many risk factors as possible.

Spinal Cord/Nerve Root Monitoring and Alert Criteria

Ongoing monitoring of the spinal cord is a recurrent process that involves frequent MEP and SSEP trials. MEP trials are run at least every 2 to 3 min and more frequently during times of high surgical risk and alerts. SSEPs are averaged approximately every 5 min. Nerve roots are monitored continuously by observing free run EMG from the respective muscle groups.

A major SSEP signal change is defined as a greater than 50% loss of amplitude. A major MEP signal change is defined as a greater than 50% loss of amplitude in 2 of 3 rectus femoris, tibialis anterior, and abductor hallucis muscles. Amplitude reductions to MEPs and SSEPs are deemed relevant when linked to a specific surgical event, and normal trial-to-trial EP variability has been excluded. Relevant amplitude changes to MEP and SSEPs should also include decreases in blood

pressure and or hematocrit. Technical, anesthetic, and systemic considerations must also be quickly assessed and ruled out.

Significant EMG activity is relevant when linked to a surgical event and sustained for greater than 10 seconds. EMG activity arising as a result of the patient being anesthetically light should be excluded.

It is imperative that significant changes to EPs be identified immediately and specific actions be taken based on the type of insult. Management of EP changes include removing or releasing offending instrumentation, increasing perfusion and oxygenation to the cord, open/close osteotomy, and exploring the surgical site for bony fragments that may be compressing the cord. Also, effective management of EP changes can be as simple as application of warm irrigation or ensuing with a brief surgical pause to allow for cord recovery. If no significant improvements are seen, then steroids, although controversial, may be administered. Finally, termination of the surgery must be considered as an option if possible.

Direct Nerve Stimulation (spondylolisthesis)

Direct nerve stimulation should be utilized for all high-grade spondylolisthesis cases. Once nerve roots are exposed, and prior to reduction of spondylolisthesis, baseline stimulation thresholds should be documented for all nerve roots at risk. Bilateral L5 and/or S1 roots are stimulated using a monopolar, cathodal stimulator with a duration of 200us. Compound muscle action potentials (CMAP) should be time-locked to the stimulus, reproducible and at least 50uA in amplitude. Stimulation thresholds are recorded from the tibialis anterior (L5) and medial gastrocnemius muscles (S1).
Stimulation thresholds should be documented again after reduction of spondylolisthesis and prior to closing. Nerve roots with significantly elevated stimulation thresholds after reduction should be re-explored for possible compression or traction injury. Decompression around the nerve root or lessening of reduction are possible responses to elevated stimulation thresholds.