Study protocol

CHIldren with neuromuscular diseases – efficacy eVALuation of spinal deformity surgeRY via different pedicle screw fixation systems study – CHIVALRY study

Contacts of the study sponsor:

Federal state budgetary institution “Russian scientific center for traumatology and orthopedics” n.a. acad. G.A. Ilizarov” of the Ministry of Health of Russian Federation, Kurgan, M. Ulyanovoy str., 6

Principal investigator:

Ryabykh Sergey Olegovich, DMSc, Head of the Axial Skeleton Pathology Laboratory and Neurosurgery Division, “Russian scientific center for traumatology and orthopedics” n.a. acad. G.A. Ilizarov” of the Ministry of Health of Russian Federation

NCT03863496 **25.12.2017**

CONTENTS

1. INTRODUCTION

1.1. Study background and substantiation

Neuromuscular diseases (NMD) — the extensive group of the genetically heterogeneous diseases, main clinical manifestations of which are weakness and atrophies of different groups of muscles. These conditions hold the first place on the prevalence of all genetic diseases of nervous system. Total prevalence of neuromuscular diseases amounts to approximately 1 on 3-3.5 thousand in different populations (Madigan R.R., 1981; Majd M.E., 1997; McCarthy R.E., 1999). National Russian register now includes more than 1200 patients. However, if we distribute this statistics to the whole Russian population, we can expect about 48 000 NMD patients in Russia. Progressive muscular dystrophies and spinal amyotrophies are the most common diseases in this group (13-33 cases per 100'000 and 10 cases per 100'000, respectively (McCarthy R.E., 1999). These groups of diseases manifest themselves always in childhood, at the age of 1-10 years (depending on the nosological entity). The course is aggressive and characterized by spinal deformity aggravation and pelvic shift ([Benson E. R. et al., 1998; Berven S., Bradford D., 2002; Wang C. H. et al., 2007; Chandran S. et al., 2011; Cheuk D.K.L. et al., 2015; Halawi M. J. et al., 2015]).

Due to the pathogenesis of neuromuscular deformity patients with such conditions have inevitable progression of spine and thorax deformity, even patients with the mature skeleton and minimal deviations (up to 20-25° by Cobb) in frontal and/or sagittal plane (Larsson E.L. et al., 2005). Early usage of rigid corset prevents significant progression at the childhood but can cause contact dermatitis and pressure ulcers. In this connection many authors insist on surgical spine stabilization at the second growth spurt (Master D.L., 2011). Patients with such conditions usually have severe and long C-type and S-type deformities with pelvic misalignment in frontal and sagittal planes. With S-type deformity body balance is often compensated, but both curves can reach 100° or more (Lonstein J., 2001). With deformity over 40° patients lose the ability to get to the vertical position and can sit only with the support. With deformity over 90° patients cannot sit (Bridwell K.H. et al., 1999; Berven S., Bradford D., 2002; Wang C.H. et al., 2007; Auerbach J.D. et al.m 2009; Ryabykh S.O. et al., 2013). Patients in a wheelchair (III functional class by GMFCS - Gross Motor Function Classification System) have high risks of severe deformities in comparison with the bed-bound patients, due to the constant axial load (Lonstein J., 2001; Teli M. et al., 2005). Frequent reference to cardiopulmonary failure as main diagnosis in autopsy results confirms that decompensated spine deformity is the main reason for premature death of such patients (Pehrsson K., 1992; Berven S., 2002; Larsson E.L. et al., 2005; Sarwark J., 2007; Chong H.S., 2011).

Duchenne muscular dystrophy patients studies showed disease progression in all patients with deformity over 40° associated with difficulties while sitting, decrease in vital capacity, decreased performance and problems with hand movements (Hsu, 1983).

Indications for surgical correction of scoliosis in patients with NMD are progressive deformity, loss of balance while seating, back pain and discomfort (Herring JA., 2002; Labelle H, 2002; Renshaw TS, 2001). Such surgery can be performed using connector systems («growing rods») (McElroy MJ, 2011; Chandran S, 2011). The main outcome of treating scoliosis is the stabilization of respiratory parameters and increase in patient activity level (Daher YH, 1985; Brown JC, 1988; Rodillo E, 1989; Phillips DP, 1989; Bridwell KH, 1999; Larsson EL, 2005).

This study will evaluate short-term and long-term effectiveness and safety of the surgical treatment in different NMD patient groups and to create precise recommendations regarding

diagnostics, approach to treatment selection and long-term management for such patients on the basis of study data

1.2. Study purpose

The purpose of this study is to evaluate efficacy and safety of spinal deformity surgery via different pedicle screw fixation systems in different groups of children with neuromuscular diseases.

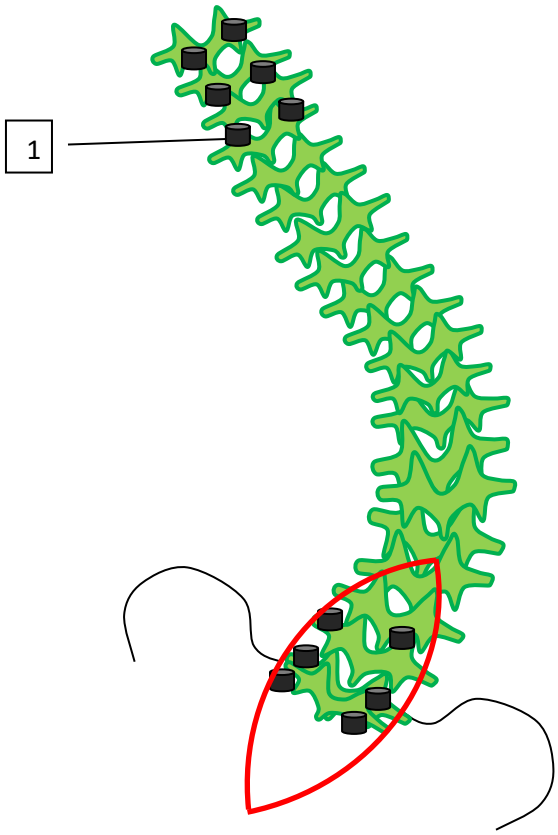
1.3. Study description

This study was sponsored by Federal state budgetary institution "Russian scientific center for traumatology and orthopedics" n.a. acad. G.A. Ilizarov" of the Ministry of Health of Russian Federation. The study will take place at this center.
It is expected to enroll 70 patients aged 10-18 years with NMD, all of whom will be subjected to thoracic and lumbar spinal deformity surgery.
Patients will be divided into two groups depending on skeletal maturity. The degree of skeletal maturity will be determined on the basis of an X-ray study of spinal and pelvic bones. The type of surgical correction will depend on the group.

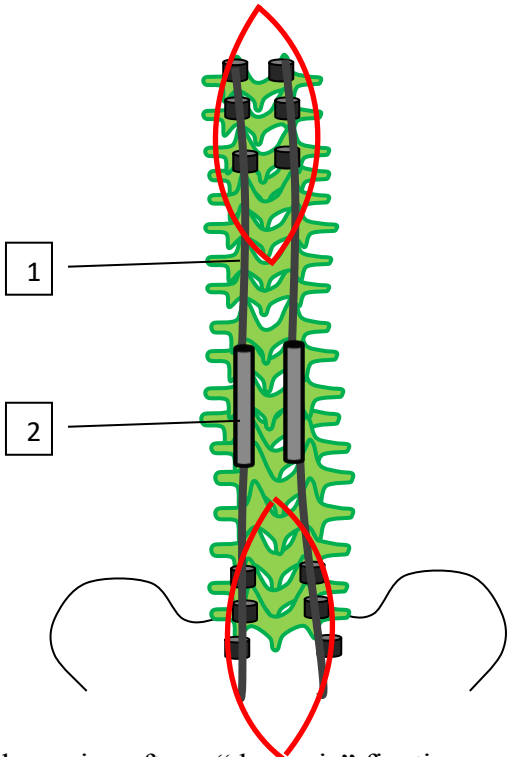
2. SYSTEM DESCRIPTION AND INTENDED SCOPE

All patients will be implanted with telescopic connector Medtronic CD Horizon Legacy 4.5 and 5.5 under X-ray control (C-arm), intraoperative spinal deformity surgery safety control (NIM Eclipse, Stealth Station S7) and standard anesthetic support.

First group of patients: local dorsal access. Cranial access: at the level of posterior Th2-5 structures and caudally at the level of L4-S2 vertebrae with exposure of posterior upper spines of iliac wings. Skeletization of vertebrae will be done within transverse processes. Pedicle support points are set bilaterally cranially at each segment level for the space of 3 segments. Caudal support base is formed with pedicle screws in lateral masses of the sacral bone or iliac crests at the level of L5-S1 vertebrae (pic. 1). Control fluorography is performed in two standard planes in order to control screw position. Two "dynamic" rods are formed on the basis of the distance between screw heads allowing 2 cm for distraction; these are two rods connected with a longitudinal connector and bent following the normal sagittal spine profile. After that, channels are formed on both sides under m. erector spinae in the cranial/caudal direction. Pre-bent rods with connectors are placed into the prepared channels. The metal construct is stabilized with internal set screws (pic. 2). If necessary, the construct may be stiffened with crosslinks. Control fluorography is performed in two standard planes in order to control implant position and evaluate correction. The intervention completes with local dorsal spinal fusion with an autobone at the level of base screws. The wound is sewn up in layers tightly.

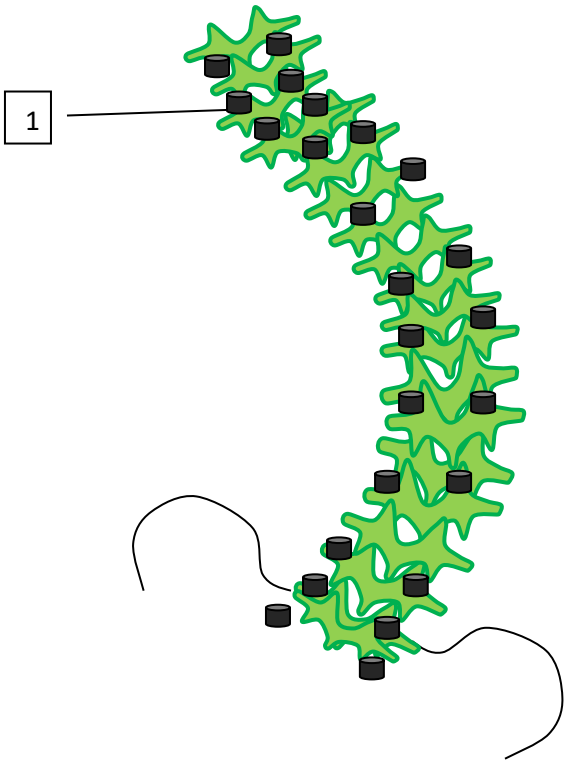


Pic. 1. Pedicle screw positioning: 1 – screw heads.

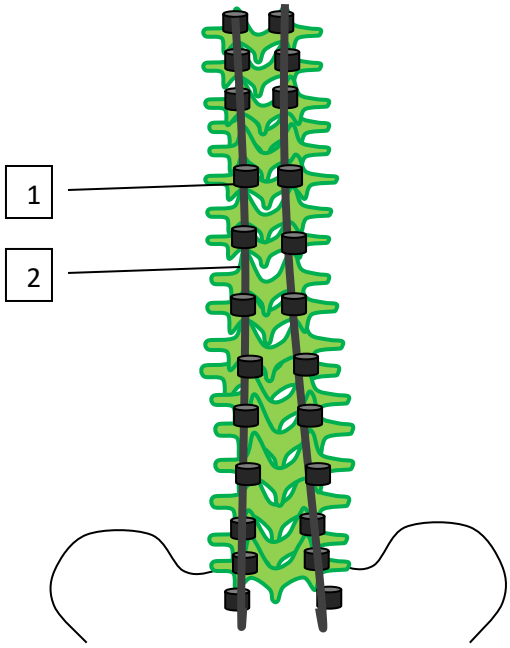


Pic. 2. Thoracic and lumbar spine after a “dynamic” fixation system has been implanted: 1 – rod, 2 – longitudinal connector.

Group two: dorsal access to the posterior column is gained in accordance with the preoperative plan. The access length depends on the instrumentation area. Vertebral skeletization is performed within transverse processes. *Subgroup 1 – pedicle support points are set bilaterally at each segment level. Subgroup 2 – pedicle support points are set bilaterally in every second segment* (pic. 3). Segmented instrumentation of 3 cranial segments to prevent dislocation of metal construct elements at the level of Th2-4 or Th3-5 vertebrae is a special measure. Similar to group I, caudal support base is formed with *pedicle* screws in lateral masses of the sacral bone or iliac crests at the level of L5-S1 vertebrae. Control fluorography is performed after that in two standard planes in order to control screw position. Segmented facetectomy is recommended for additional spine mobilization. Pre-bent rods are placed into support points. Deformity correction is performed by means of a translational maneuver, segmented distraction (concave side) and compression (convex side). The metal construct is stabilized with internal set screws (pic. 4). If necessary, the construct may be stiffened with crosslinks. Control fluorography is performed in two standard planes in order to control implant position and evaluate correction. The intervention completes with dorsal spinal fusion with an autobone along the implants. The postoperative bed is subjected to Redon drain. The drainage is exteriorized to the skin via a separate puncture. The wound is sewn up in layers tightly.



Pic. 3. Screw positioning via pedicles: 1 – screw heads.



Pic. 4. Thoracic and lumbar spine after a fixation system has been implanted: 1 – screw heads, 2 – rod.

3. STUDY PLAN

3.1. Study goals and objectives

1. To estimate effectiveness and safety of surgical treatment for spinal deformities with different pedicle screw fixation (PSF) systems in various pediatric patient groups with neuromuscular diseases

2. Considering patient condition, deformity progression, age, physical, motor, cognitive, functional, static and dynamic status present the following:

a) Develop diagnostic algorithm for patients with severe deformities of thoracic and lumbar spine following NMD
b) Create surgery planning algorithm: instrumentation area planning, number and location of fixation points planning, grounds for spine mobilization and area of mobilization
c) Assess effectiveness of the intraoperative safety control technologies - navigation and monitoring during surgical treatment of spinal deformities in NMD patients (Nim Eclipse, Stealth Station S7)
d) Evaluate dynamics in physical, static, dynamic and functional status after surgical treatment using special scales

We assume that the study will result in the following:
- introduction of modern surgical methods of treating children with severe spinal deformities at NMD;

- development and simulation of individual methods of surgery and spinal system elements for treating children with severe spinal deformities at NMD.

3.2. Endpoints

The primary endpoint is decrease in spine deformity grade by 1 or more (according to Chaklin classification) with stabilization or improvement in lung parameters in 12 months after the surgery.

Secondary endpoints are as follows:

1. Hospitalization by all causes
2. Improvement in life quality after surgery according to scales (VAS, GMFCS, RLAS, FIM, MACS) in 6 months and 12 months after surgery.

3.3. Study design

This study is prospective, non-randomized, single-center, open and non-comparative; it involves two parallel groups of patients (children aged 10-18 years) with severe thoracic and lumbar spinal deformities at NMD.

Patients are divided into groups depending on skeletal maturity determined on the basis of an X-ray study of spinal and pelvic bones. The type of surgical correction will depend on the group.

1. Group of patients with spinal deformities corrected and stabilized with bilateral connector systems (growing skeleton).

Bone maturity grades I-III (Sadofyeva classification) or I-II (Risser classification).

Bilateral connector systems ("growing rods") will be used in this group (N = 30).

2. *Group of patients with spinal deformities corrected and stabilized with bilateral multiple fixation points (mature skeleton).*

Bone maturity grades IV-V (Sadofyeva classification) or III-IV (Risser classification).

Inside this group (N=40) two subgroups are planned depending on varying anatomic characteristics thus allowing for specific treatment option:

- *Subgroup 1 – segmental fixation*
- *Subgroup 2 – intermittent (next nearest) segment fixation*

Patients will be enrolled in study groups in consecutive stages, according to enrollment criteria described above

3.4. Patient population

The targeted population of this study includes underage patients of both male and female aged 6-25 years with neuromuscular diseases (spinal atrophies, myopathies, myodystrophies).

3.5. Study duration

The follow-up period for each patient will be at least 12 months. Enrollment of patients will continue for 24 months. The expected total study duration is 36 months (12 months after enrollment of the last patient).

3.6. Inclusion/exclusion criteria

A patient should meet the inclusion criteria and lack all exclusion criteria to be considered.

Inclusion criteria:

1. Signed and dated informed consent for participation in the study (separate informed consents for child and parents/caregivers), obtained before conducting any study procedures
2. Age from 6 to 25 years

3. Male and female patients
4. Verified and documented diagnosis with the results of neurologic examination
5. Deformity of thoracic and/or lumbar spine associated with NMD, which requires surgical intervention

Exclusion criteria:
1. Patient unwillingness or inability to follow study procedures
2. Absence of signed and dated informed consent for participation in the study (as for child and for parents/caregivers)
3. Patient participation in another clinical study, which can influence the results of this study
4. Life expectancy <12 months
5. Concomitant diseases, which preclude patient participation in this study according to doctor's opinion

Participant exclusion criteria:
Patients may be excluded from the study at any time. The reasons for exclusion may be as follows:
1. Voluntary patient withdrawal (consent withdrawal for any reason or without giving a reason) without negative effects on further treatment.
2. Failure to follow-up a patient.

3.7. Data collection
Clinical data will be collected at certain time points of this study. The requirements to data collection and study visit schedule are given in table 1.

Table 1: Study stages and procedures

Stages / Procedures	Screening	Distribution into groups and surgery	Postoperative period (early observation: 24-48 hours)	Before discharge (ca. after 21 days)	6 months post operation ± 14 days	12 months post operation ± 30 days
	Visit No. 1	Visit No. 2	Visit No. 3	Visit No. 4	Visit No. 5	Visit No. 6
Informed consent	X					
Anamnesis morbi	X					
Physical examination, evaluation of orthopedic, somatic and neurological status	X	X	X	X	X	X
Evaluation of quality of life (GMFCS, RLAS, FIM, MACS)	X				X	X
X-ray[1]	X			X	X	X
Intraoperative control efficacy evaluation		X				

Clinical blood analysis[2]	X		X	X		X*
Biochemical blood analysis[3]	X		X			X*
Spirometry*	X					X*
EchoCG*	X					X
CT[4]	X			X		X**
MRI[5]	X					
Documentation of serious adverse events		X	X	X	X	X

1. Spinal X-ray (from Th1 to S4), 2 standard projections.
2. RBC, hematocrit, hemoglobin, WBC, thrombocytes, ESR.
3. Total protein, creatinine, urea, bilirubin, AST/ALT, glucose.
4. Spine CT (from Th1 to S4).
5. MRI of the spine and the spinal cord.
** Performing research only for medical reasons;*
*** If there are signs of a bone block in the area of instrumental fixation according to the radiograph of the spine*

3.8. Study procedures and visit schedule

A patient and his/her parent/parents should sign separate forms of informed consent to participation in the study before any study-related procedures.

Study procedures will be performed in accordance with the current standards of care. Procedures, evaluations and examinations not listed in the visit schedule might be performed at discretion of an attending physician in accordance with standards of medical care of the healthcare institution and patient safety requirements.

The study consists of the following stages:
• Signing of informed consent forms (separate informed consent forms for parents and the child)
• Screening
• Distribution into groups and surgery
• Early observation (24-48 postoperative hours)
• Discharge (ca. after 21 days)
• Follow-up 6 months after the operation
• Long-term follow-up – 12 months after the surgery performed

3.8.1. Procurement of informed consent from patients

The investigator should see to it that the patient's parents have received complete and adequate information on the main points of the study, its objectives, possible risks and benefits of participation verbally or in writing. The patient's parents should also be informed that they might voluntarily withdraw their child from participation in this study at any time. The patient's parents should be given the opportunity to ask questions and time for consideration.

The informed consent form signed by the patient's parents (signature of one of the parents will suffice) should be obtained before any study-related procedures.

The children who were offered to take part in the study should also be given information on the study considering their abilities to understand such information, sign and date written informed consent (a separate informed consent form) with their own hand.

The investigator should keep original informed consent forms signed by patients and their parents. Copies of the signed informed consent forms should be given to patients and their parents.
Any changes to the previously approved informed consent form during the study should be reapproved by the LEC.

3.8.2. Enrollment of patients in the study and screening

A patient is considered a study participant only after informed consent forms have been signed by a patient and their parents.
The screening visit (visit No. 1) consists of the following procedures:

- patient history;
- physical examination and clinical evaluation: physical status (body mass index);
- functional status and life quality (with VAS, FIM, MACS, GMFCS);
- Spine X-ray: scoliotic and kyphotic deformity measurements (Cobb angle), static and dynamic imbalance in frontal and sagittal planes;
- laboratory tests: clinical blood analysis, blood chemistry;
- spirometery, ECG, echocardiography;
- spine CT with the assessment of structural vertebral changes;
- MRI of the spine and spinal cord.

3.8.3. Visit No. 2. Distribution into groups and surgery

Distribution into study groups will be performed according to the results of physical examination and the evaluation of orthopedic, physical, and neurologic status and serious adverse events. Surgical correction will be performed with standard anesthesia and intraoperative safety control during deformity correction – with navigation and monitoring system, according to hospital's standards of care

3.8.4. Visit No. 3. Early observation (24-48 hours)

The following study procedures will be performed 24-48 hours after surgery (index procedure):
- Physical examination;
- Laboratory analysis: clinical blood analysis, blood chemistry;
- Evaluation of severe adverse events (if any).

3.8.5. Visit No. 4. Before discharge (ca. after 21 days)

The duration of inpatient stay is determined by standards of the healthcare institution and on the average amounts to 21 days (depending on the patient's clinical condition). The following study procedures will be performed before discharge:
- Physical examination;
- spine X-ray: scoliotic and kyphotic deformity measurements (Cobb angle), static and dynamic imbalance in frontal and sagittal planes;
- Spine CT and verification of screw position;
- laboratory tests (clinical blood analysis, blood chemistry);
- documentation of serious adverse events.

3.8.6. Visit No. 5. 6 months after the surgery

The following study procedures will be performed during a scheduled visit 6 months after the procedure:
- physical examination and clinical evaluation: physical status (body mass index);
- functional status and life quality (with VAS, FIM, MACS, GMFCS);
- spine X-ray: scoliotic and kyphotic deformity measurements (Cobb angle), static and dynamic imbalance in frontal and sagittal planes;
- documentation of serious adverse events.

3.8.7. Visit No. 6. 12 months after the procedure

The following study procedures will be performed during a scheduled visit 12 months after the procedure:
- physical examination and clinical evaluation: physical status (body mass index);
- functional status and life quality (with VAS, FIM, MACS, GMFCS);
- spine X-ray: scoliotic and kyphotic deformity measurements (Cobb angle), static and dynamic imbalance in frontal and sagittal planes;
- laboratory tests (clinical blood analysis) (as an option if there is a medical condition);
- spirometery, ECG, echocardiography (as an option if there is a medical condition);
- Spine CT with evaluation of screw position and fusion mass (as an option, if there are signs of a bone block in the area of instrumental fixation according to radiographs of the spine);
- documentation of serious adverse events.

3.8.8. Unscheduled visits

Unscheduled visits – NMD-induced spinal deformity-related visits not required by the study protocol.
If a patient had an unscheduled follow-up visit, the data obtained during such a visit are recorded separately.

3.8.9. Study withdrawal

Patients may withdraw from the study in the following situations:
• The follow-up period has completed;
• A patient is not available to follow-up;
• Patient death;
• A patient decided to withdraw from the study (refused to continue participation, moved to a different region);
• The investigator deemed patient withdrawal from the study necessary (for example, due to medical reasons or impossibility of adequate patient compliance with protocol requirements).

If a patient is considered not available to follow-up or refuses to continue participation or the investigator deems patient withdrawal from the study necessary, the investigator shall document patient withdrawal and the reason for withdrawal. After a patient has withdrawn from the study, further data collection and additional visits are not performed.
After their withdrawal from investigation, a patient will still obtain the normal treatment comparable with that as rendered during the regular surgical correction.

4. REGULATORY COMPLIANCE

Design of this study was developed in compliance with principles of the Good Clinical Practice (GCP) described in ISO 14155:2011 and requirements of ISO 14155-1-2008 “Clinical investigation management of medical devices.”

Ethics review of study documents and further ethics support of the study will be conducted by the Local Ethics Committee (LEC) at at Federal state budgetary institution "Russian scientific center for traumatology and orthopedics" n.a. acad. G.A. Ilizarov" of the Ministry of Health of Russian Federation.
The study will be conducted in accordance herewith, current legislation of the Russian Federation and LEC requirements as governed by principles of the Declaration of Helsinki.

5. SEVERE ADVERSE EVENTS

Information on all severe adverse events (SAE) will be collected throughout the study.
Severe adverse event (SAE) – a medically unfavorable event (adverse event) resulting in one of the following:
a) Fatal outcome;
b) Major aggravation of patient's health due to:
1) a life-threatening disease or injury, or
2) a persistent function impairment or structural damage, or
3) a condition requiring hospitalization or increased duration of inpatient stay;
4) a condition requiring additional therapeutic intervention or surgery to prevent a life-threatening disease or injury.

Information on SAE will be collected throughout the study from the moment of signing the informed consent form. Reports on these effects will be sent to the LEC. These reports will contain the following information:
• Date of the SAE;
• Description of the SAE;
• Treatment of the SAE;
• Outcome;
• Evaluation of severity of the SAE and its connection with the index procedure.

The type and duration of SAE observation will depend on its classification; treatment will be conducted at the investigator's discretion. Patients will be followed up until SAE are resolved, patients withdraw from the study or the study is completed, whichever is the soonest. If a patient withdraws from the protocol before the study is completed, maximum efforts will be made to continue following a patient up until SAE are resolved or deemed persistent without the need in further action.

6. STATISTICAL ANALYSIS AND METHODS

Primary and additional quantitative efficacy and safety criteria will be summarized in shift tables and presented by means of descriptive statistics; the appropriate methods will be selected depending on the data. Missing data will be indicated as N/A and not considered in aggregate statistics. The significance of differences between data groups will be evaluated using the criteria depending on the number of observations and distribution type of parameter values within groups. Software: Statistical Package for the Social Sciences (SPSS), v. 22.0 (SPSS Inc., Chicago, IL, USA). T-criteria: 1) comparison of correction of sagittal and frontal spinal deformity components with graded FC parameters. Differences will be considered significant if two-sided $p < 0.05$.

7. REPORT AND DATA PUBLICATIONS

Intermediate reports are planned to be provided to Medtronic and the LEC throughout the study. Upon completion of the study all study data will be analyzed and a final study report drawn to be provided to Medtronic and the LEC. Study results are also intended to be published and presented at professional events having the materials preliminarily approved by Medtronic. The expected time of publication of final results – 2020-2021.
The study will be registered at the international resource for clinical trials: www.clinicaltrials.gov.