CLINICAL STUDY PROTOCOL

MISCOS-Minimal Invasive SColiosis or Open Surgery

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Research Body:	Akademiska University Hospital Uppsala and Uppsala University
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SYNOPSIS

Rationale for conducting the study:
The operative treatment of idiopathic scoliosis typically involves a posterior correction with fixation by open surgery with simultaneous fusion of the operated levels. That type of surgery, although it leads to an almost anatomical correction, involves a long hospitalization time due to extensive tissue damage and pain. Recently, however, by using various regimes such as "ERAS" (enhanced recovery after surgery), including optimization of pain relief, inpatient stay times have been heavily reduced, and discharge as early as 1-2 days after surgery is now possible to achieve.

In recent years, there has been a development of minimally invasive techniques in spine surgery where tissue damage and blood loss are significantly minimized. It is of importance to scientifically investigate whether the use of minimally invasive techniques also in scoliosis surgery results in benefit for patients.

We need to investigate whether minimally invasive techniques are comparable to traditional open surgery in terms of reoperations, serious adverse events, infections, pain and radiologically healed fusion. One complexity of minimally invasive surgery (MIS) lies in the correct placement of implants in the deformed spine while preserving the tissue and not exposing the anatomical landmarks that usually guide for correct screw placement. It is why MIS practically entails the use of intraoperative 3D imaging or robotic assisted surgery (RAS) to improve screw placement accuracy.

The aim with this project is to evaluate whether MIS is non-inferior to the traditional open technique regarding reoperations, serious adverse events, infections, pain and radiologically healed fusion. At the same time, we want to compare the aforementioned techniques regarding inpatient stay, degree of correction, screw placement, neurophysiological incidences, blood loss, operation time, and patient related outcomes (PROMs).

As of yet, the majority of data in this area are based on retrospectively collected series, and some prospectively collected series, while randomized controlled trials are lacking.

Study design: Multicenter randomized controlled clinical trial.
Study population: Individuals with spinal deformity aged 10 through 25 years.
Number of individuals: 180

Inclusion criteria:
- Written informed consent
- Idiopathic scoliosis
- Age between 10-25 years
- Posterior correction for scoliosis
- Major curve Cobb angle 75 degrees or less

Exclusion criteria:
- Inability to give informed consent
- Other diagnosis of scoliosis than “idiopathic”

- Rigid curves that require posterior or three-column osteotomy/ies
- Previous surgery at the operated levels
- BMI > 35
- Psychological factors that make the patient unsuitable for inclusion in the study (e.g., substance abuse, developmental disability)

Study inclusion period:
Mid 2025-mid 2028

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
RCT	Randomized Controlled Trial
MIS	Minimal Invasive Surgery
RAS	Robotic Assisted Surgery
3D	Three-dimensional
Swespine	Swedish Spine registry
CT	Computed Tomography
SRS-22r	Scoliosis Research Society 22 revised
EQ-5D-3L	EQ-5D three level
ODI	Oswestry Disability Index
EOSQ-24	Early Onset Scoliosis Questionnaire 24
SSI	Surgical Site Infection
CBCT	Cone Beam Computed Tomography

1. INTRODUCTION

1.1 Background

Idiopathic scoliosis is the most common type of spinal deformity with an overall prevalence of 1.9-3.0% and one of the most common reasons for extensive and complicated surgical treatments at youth. Beside the difficulties/challenges of treatment and the high cost for the healthcare system it can have a major impact on the quality of life of patients, both at the young age and later in life.

Proper recognition and treatment of idiopathic scoliosis helps to optimize patient outcomes. Treatment of idiopathic scoliosis depends on the curve size, curve progression and skeletal maturity. A Cobb curve angle greater than 45 degrees in skeletally immature individuals and 50 degrees in skeletally mature individuals are usual indications for surgery.

The operative treatment of idiopathic scoliosis typically involves a posterior correction with fixation by open surgery with simultaneous decortication of the operated levels. This type of surgery, although it leads to an almost anatomical correction, involves a long hospitalization time due to extensive tissue damage and pain. Recently, however, by using various regimes such as "ERAS" (early rehabilitation after scoliosis surgery) and by optimization of pain relief, reports of as short inpatient stay as 1-2 days exists.

In recent years, there has been an evolutionary development of minimally invasive techniques in spine surgery where tissue damage and blood loss are significantly minimized. It is therefore of great importance to scientifically investigate whether such a minimally invasive technique will mean even greater benefit for patients with an even shorter hospitalization and overall convalescence time.

At the same time, we need to investigate that the minimally invasive technique is not inferior compared to open surgery. One complexity of minimally invasive surgery (MIS) lies in the correct placement of implants in the deformed spine while preserving the tissue and not exposing the anatomical landmarks that usually guide for correct screw placement. This is why MIS practically entails the use of intraoperative 3D imaging and in some cases robotic assisted surgery (RAS) to achieve a high screw placement accuracy.

The primary aim with this project is to evaluate whether MIS is non-inferior to traditional open technique in terms of reoperations, serious complications, surgical site infections, pain and fusion rate in the long term. Moreover, we set out to compare the aforementioned techniques with regard to hospitalization time, accuracy of screw placement, neurophysiological incidences, blood loss, operation time, and patient related outcome measures (PROMs).

As of yet, the majority of data in this area are based on retrospectively collected series, and some prospectively collected series, while randomized controlled trials on spinal deformity are lacking. While MIS has rapidly developed in the field of degenerative spine surgery, it is important to investigate whether MIS in patients with idiopathic scoliosis could minimize inpatient stay and pain and at the same time not compromise other factors of a “successful” operation such as the degree of correction and fusion.

1.2 Ethical issues

We think it is important to evaluate the use of MIS in scoliosis patients because it may lead to better outcomes regarding reoperations, overall rehabilitation, infection rates, blood loss and inpatient stay. MIS techniques are already used widely in degenerative spine surgery as well as in spinal trauma and are well-established.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary objective

Study design

This is a multi-center non-inferiority two arm randomized controlled trial. Results of MIS are expected to be non-inferior in terms of reoperations, serious complications, surgical site infection, pain and fusion rates compared to open surgery.

Definition of MIS:

Minimal invasive surgery (MIS) is here defined as a muscle salvage technique. Minimal invasive surgery is defined such that the posterior elements of the spine are not exposed and the spinal musculature is not detached from the posterior elements of the spine. That means that the erector spinae musculature is not detached from the spinous processes and the laminae, except for the exposure needed for the actual screw insertion. The surgeon is free to use either a long incision or multiple short incisions.

The arms consist of:

1. *Intervention group*
   Patients operated with MIS: Minimal invasive surgery. The surgeon will be free to choose the method of screw placement. 3D-navigation, RAS, free hand technique or combinations of these may be used for screw placement. A long skin incision and subcutaneous multiple incisions are performed. The erector spinae musculature is not detached from the spinous processes and the laminae, except for the exposure needed for the actual screw insertion. Each screw is inserted through an incision in the musculature. The surgeon may choose to do decortication of all or some of the facet joints in the surgical area.

2. *Control group*
   Patients operated with open surgery: Traditional open surgery. The surgeon will be free to choose the method of screw placement. 3D-navigation, RAS, free hand technique or combinations of these may be used for screw placement. A long skin and subcutaneous incision is performed. The posterior elements of the spine are exposed and the spinal musculature is detached from the posterior elements of the spine. The whole surgical area is exposed and all screws are inserted through this area. Separate incisions for screw placement in the musculature are not needed. The surgeon may choose to do decortication of all or some of the facet joints in the surgical area.

Preoperative planning

Planning of the surgery includes planned implant placements and levels of surgery on an AP and sagittal x-ray or preoperative low-dose CT. Operative planning is an important part of all surgeries that will be specifically documented before surgery. Planning includes the specification of each vertebra and pedicle that will be used for implant placement and is documented on a specific protocol before surgery called “Operation protocol MISCOS clinical trial” (see Appendix).

Primary endpoint

The primary endpoint is the assessment of a group of variables by the statistical method of “win odds”. The variables are in hierarchic order:

i. No reoperations at 2 years after surgery. A reoperation is defined as a secondary surgical procedure related to the index procedure and involving the spine at any level after the index procedure.
ii. No serious complication related to the procedure. Serious complication is defined as a life-threatening complication or a complication related to substantial invalidity (like pneumothorax or spinal cord injury).
iii. No early surgical site infection (SSI). Early SSI is defined as SSI with onset up to 12 weeks postoperatively.
iv. No other infection related to the inpatient stay like pneumonia or urinary tract infection (UTI).
v. Assessment of pain at 2 years f-u: The numeric rating scale (NRS) for back pain will be used measured on a scale from 0 (no pain) to 10 (worst possible pain). Data will be collected from Swespine or similar platforms.
vi. Assessment of SRS-22r: The SRS-22r is a scoliosis specific questionnaire aiming to estimate quality of life in patients with scoliosis [1]. It contains 24 items divided into 5 domains covering function, pain, self-image, mental health, and satisfaction. An index value is calculated for each domain and a total index value is possible to calculate ranging from 1 (worst) to 5 (best). SRS-22r will be collected from Swespine or similar platforms at 2 years.
vii. Radiologically healed fusion at 2 years f-u. A radiologically healed fusion is defined as bone bridging along the originally operated levels. A vertebral segment will be considered fused if one or both of the following conditions is satisfied:
    a. Bone bridge over at least one facet joint
    b. Bone bridge between the vertebral bodies

2.2 Secondary objectives

The following secondary objectives will be studied in comparisons between MIS and open operating procedures.

Secondary objectives related to the patient

- Inpatient stay

Secondary objectives related to operative technique

- Deformity correction rate assessed as Cobb-angle correction in a postoperative x-ray from the first standing radiograph compared to the last preoperative radiograph. The correction of the curve will be calculated according to the formula: (preoperative Cobb angle - postoperative Cobb angle) / (preoperative Cobb angle) × 100%.
- Progression of Cobb angle in the operated levels at 2-years standing AP/PA x-ray compared to the 3-month standing AP/PA x-ray.
- Progression of secondary curves at 2 years f-u compared to the 3-month x-ray.
- Perioperative blood loss.
- Technical accuracy of screw placement at first attempt.
- Total procedure time (from incision to closure) as well as normalized to number of spinal levels from the upper to the lower instrumented vertebra.
- Accuracy of screw placement at first attempt (see 6.2)
- Intraoperative neurophysiological monitoring (see 6.2). Any incidences are recorded.

Secondary objectives related to patient surgical & postsurgical characteristics

- Postoperative characteristics
  - Costs per patient. Total cost per patient during the first 2 years of the study including cost of possible re-admissions and reoperations related to index surgery. Data on costs on the individual level will be collected. These consist of costs for the inpatient and outpatient visits (including surgery, radiographs, navigation), analgesic and antibiotic treatments as well as possible re-admissions related to index surgery.
- Patient reported outcome measures (see 6.2)

3 STUDY DESIGN AND PROCEDURES

3.1 Overall study design and flow chart

This is a multi-center parallel assignment two arm randomized controlled trial (Figure 1). The trial will use a pragmatic approach and use existing equipment and document handling at the participating centers. Data from the existing quality registries for spine surgery will be extracted for outcome assessments.

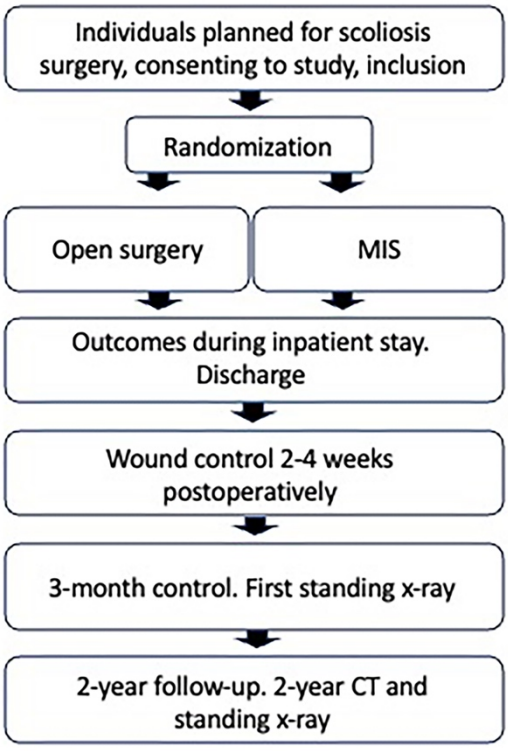
Randomization between the two treatment arms will take place approximately a week preoperatively, as close to the operation day to minimize selection bias. Postoperative, blinding of the patients and health care personnel will be done.

The surgeons will be the only personnel related to patient follow-up that will not be blinded. However, the majority of the analyses, all postoperative imaging and record data collection and analysis will be performed by blinded reviewers.

Patient reported outcomes will be assessed without influence of the care giver.

The Uppsala University hospital performs approximately 80 spine deformity surgeries yearly and it is estimated that ¼ of these meet the inclusion criteria for the study. Similar estimations are done for the rest of the centers with a total enrolment of approximately 50 patients per year. Our time plan includes study start (mid 2025), last patient included (2028) and last 2 year follow up (2029). Registry outcome data are collected preoperatively, at 1 year and 2 years. Registry data may also be collected at 5 and 10 years. The study may have come to an end 2038. However, delays in studies such as these are not uncommon.

Figure 1: Flowchart



3.2 Rationale for study design

We will use a randomized controlled trial design to minimize selection bias and we aim to study advantages and disadvantages of MIS in relation to open approach in scoliosis surgical correction. The study uses a pragmatic approach and uses already available surgical techniques and infrastructures, such as already applicable minimal invasive approaches and existing navigation systems, hospital and quality registries, and picture archiving and communications systems.

Randomization to MIS or open surgery will be done within the Swespine registry-platform or in RedCap. Randomization will be stratified by country. Randomization lists will be prepared in advance by an independent statistician or data manager and will be concealed for the researchers.

Study visits are shown in Table 1. Patients will be assessed before surgery, during surgery and inpatient stay, at 3 months, 2 years and through the Swespine registry at 1, 2, 5 and 10 years. There will also be a 2-4 week surgical wound control by the health care personnel. There will be no additional visits for the patient involved in the study compared to the clinical routine.

Table 1. *Study activities.*

Day:	Visit 1 Screening *Initial visit*	Visit 2 *Inpatient stay/surgery*	Visit 3 *outpatient clinic by Health care personnel* 2-4 weeks	Visit 4 *3 months*	Visit 5 *2 years*
Informed consent	X				
Demography	X				
Inclusion/exclusion criteria	X				
Randomization		X***			
Surgical wound control			X		
Standing x-rays	X			X	X
2-year low-dose CT and standing x-ray control					X
Outcome assessments	X	X	X*	X**	X**

*Outcomes related to wound control (SSI)

**Outcomes assessed at regular clinical follow-ups; complications, SSI, readmissions and reoperations. SRS-22r, EOSQ-24, ODI, EQ-5D-5L questionnaires collected as per Swespine routine on web or paper (preop, 1, 2, 5 and 10 year postop).

*** Randomization will be done approximately a week prior to operation

4 STUDY POPULATION

4.1 Inclusion criteria

- Written informed consent
- Idiopathic scoliosis
- Age between 10-25 years
- Posterior correction for scoliosis
- Major curve Cobb angle 75 degrees or less

4.2 Exclusion criteria

- Inability to give informed consent
- Other diagnosis of scoliosis than “idiopathic”
- Rigid curves that require posterior or three-column osteotomy/ies
- Previous surgery at the operated levels
- BMI > 35
- Psychological factors that make the patient unsuitable for inclusion in the study (e.g., substance abuse, developmental disability)

4.3 Subject enrollment and randomization

Individuals scheduled for spinal deformity surgery will be informed of the study at the time of an outpatient visit.

Subject eligibility will be established before treatment randomization. Subjects will be randomized sequentially approximately a week before operation, as subjects are eligible for randomization. If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.

4.4 Discontinuation and withdrawal of subjects

Subjects are free to discontinue their participation in the study at any time. This will not affect further treatment. Patients will be withdrawn from study if the patient withdraws consent. Already collected study data for these patients will be kept in the study database, however new data, including data from registries will not be added.

4.4.1 Premature termination of the study

The study group may decide to stop the trial or part of the trial at any time. Furthermore, the investigator should promptly inform the Ethics Committee and provide a detailed written explanation.

4.5 Re-screening

Re-screening for study inclusion is allowed before surgical treatment has been performed.

5 STUDY TREATMENTS

All treatments involve surgical stabilization and fusion of the deformed spine.
All forms of treatment are available and used today. The choice and use of 3D-imaging, navigation and RAS, or freehand are based on the preference of each surgeon. Navigated placement of pedicle screws is done according to local routines. Intraoperative cone beam computed tomography (CBCT) or preoperative low-dose CT can be used. The choice of supplier and brand of spine implants are based on the preference and availability in each center.

5.1 Minimal invasive scoliosis surgical correction- intervention group

Patients operated with MIS: Minimal invasive surgery. The surgeon will be free to choose the method of screw placement. 3D-navigation, RAS, free hand technique or combinations

of these may be used for screw placement. A long skin incision and subcutaneous multiple short incisions are performed. The erector spinae musculature is not detached from the spinous processes and the laminae, except for the exposure needed for the actual screw insertion. Each screw is inserted through an incision in the musculature. After placement of the screws, the positioning is checked with an intraoperative computed tomography. Misplaced screws may be repositioned or extracted. After implant placement, rods are bent to the desired shape and placed. Correction of the deformity and fixation is performed.

The surgeon may choose to do decortication of all or some of the facet joints in the surgical area. Decortication is performed by a navigated high-speed burr or other technique in a minimally invasive way. Finally, the wound/s is/are closed.

5.2 Open scoliosis surgical correction- control group

Patients operated with open surgery: Traditional open surgery. The surgeon will be free to choose the method of screw placement. 3D-navigation, RAS, free hand technique or combinations of these may be used for screw placement. A long skin and subcutaneous incision is performed. The posterior elements of the spine are exposed and the spinal musculature is detached from the posterior elements of the spine. The whole surgical area is exposed and all screws are inserted through this area. Separate incisions for screw placement in the musculature are not needed. After placement of the screws, the positioning is checked with an intraoperative computed tomography. Misplaced screws may be repositioned or extracted. After implant placement, rods are bent to the desired shape and placed. Correction of the deformity and fixation is performed. The surgeon may choose to do decortication of all or some of the facet joints in the surgical area. The surgeon may choose to do decortication of the spinous processes and laminae in the surgical area. Decortication is performed by a high-speed burr or other technique. Finally, the wound is closed.

5.3 Pre- and perioperative 3D-imaging, navigation and RAS

Navigation is done based either in intraoperative computed tomography, surface matching, augmented reality surgical navigation or infrared surgical navigation. Surface matching and infrared surgical navigation are based on the recognition and require detection of optical markers on a reference frame attached to a bony prominence of the spine. Augmented reality surgical navigation will show the entry point and direction of the planned screws on an augmented reality image screen in the operating theater.

In the end, navigation will result in a three-dimensional image of the spine in which screws are placed according to one of the following methods:

- The surgeon places the screws manually following the image and the virtual screw placement on the screen
- The surgeon places the screws through a robotic arm [Robotic Assisted Surgery (RAS)]. Prior to screw placement the surgeon plans the position of the screws on the preoperative low dose CT or the perioperative CBCT.

- If the surgeon prefers to use the free hand technique in combination with an intraoperative computed tomography verification of screw positioning, or other means to identify screw placement this is also possible.

5.4 Blinding

The study design does not allow blinding of the surgeons and other personnel in the operating theatre. However, the patient and other health-care personnel will be blinded and held up to two years postoperatively. Patient reported outcomes will be assessed without influence of the caregiver.

5.5 Randomization

The subjects are randomized in a 1:1 ratio, for MIS or open technique treatment arms. Randomization will be performed through the web-based platform of the Swespine registry (or similar platforms like RedCap) using an allocation sequence hidden from the healthcare personnel and provided independent from the study. Block randomization will be used. Block sizes will be unknown for the researchers. The inclusion will end when the sample size has been reached in both intervention arms.

5.5.1 Technical problems encountered during surgery

If a technical problem with the 3D/navigation system or RAS system is encountered during surgery, the patient will be kept in the group to which he or she was randomized. This means that a possible MIS approach needs to be converted to open technique to enable screw placement by free hand technique. The patient will remain in the group to which he or she was randomized to and will not be replaced.

5.6 Concomitant medication

Patients will receive their ordinary medications and the standard pre- and postoperative treatment.

5.7 Surgical data and complications

Detailed surgical data will be collected through hospital files, radiographs, Swespine or similar platforms. Additional spine surgeries (diagnosis and type of surgical procedure) will be identified in Swespine (or similar platforms) and the hospital files. Adverse events (postoperative infection, deep vein thrombosis and pulmonary emboli) will be collected from the hospital files and Swespine.

5.8 Imaging

Normal imaging and time points are as follows: Standard preoperative investigations include a whole spine standing radiograph, a whole spine bending radiograph and magnetic resonance imaging (MRI) of the spine. A preoperative low-dose CT or an intraoperative CBCT is always performed prior to screw placement. Screw placement is verified by a CBCT intraoperatively. The minimum radiologic follow-up includes a whole spine standing radiograph at the 3-month follow-up and a low-dose CT along with a standing radiograph at the 2-year follow-up. Curve size, type of scoliosis and other radiological parameters will be registered.

6 STUDY MEASUREMENTS AND VARIABLES

6.1 Primary variables

1. Reoperation within 2 years: A reoperation is defined as a secondary surgical procedure related to the index procedure and involving the spine at any level after the index procedure.
2. Serious complication: A life-threatening complication or a complication related to substantial invalidity (like pneumothorax or spinal cord injury).
3. Early SSI. It is defined as SSI with onset up to 12 weeks postoperatively.
4. Other systemic infection related to inpatient stay: Like pneumonia or UTI
5. Pain at 2 years f-u will be assessed with the numeric rating scale (NRS) for back pain measured on a scale from 0 (no pain) to 10 (worst possible pain). Data will be collected from Swespine or similar platforms.
6. SRS-22r: The SRS-22r is a scoliosis specific questionnaire aiming to estimate quality of life in patients with scoliosis [1]. It contains 24 items divided into 5 domains covering function, pain, self-image, mental health, and satisfaction. An index value is calculated for each domain and a total index value is possible to calculate ranging from 1 (worst) to 5 (best). SRS-22r will be collected from Swespine or similar platforms.
7. Radiologically healed fusion: A radiologically healed fusion is defined as bone bridging along the operated levels according to the preoperative plan. A vertebral segment will be considered fused if one of the following conditions is satisfied:
    a. Bone bridge over at least one facet joint
    b. Bone bridge between the vertebral bodies

6.2 Secondary variables

The secondary variables are listed below.

1. Inpatient stay in days.
2. The deformity correction rate will be assessed as Cobb-angle correction in a postoperative x-ray from the first standing radiograph compared to the last preoperative radiograph. The correction of the curve will be calculated according to the formula: (preoperative Cobb angle - postoperative Cobb angle) / (preoperative Cobb angle) × 100%.
3. Progression of Cobb angle in the operated levels at 2-years standing x-ray compared to the 3-month (first follow-up) x-ray. The progression of the curve will be calculated according to the formula: (2-year Cobb angle - 3-month Cobb angle) / (2-year Cobb angle) × 100%.
4. Progression of secondary curve angles at 2-years standing x-ray compared to the 3-month (first follow-up) x-ray. The progression of the curve will be calculated according to the formula: (2-year Cobb angle - 3-month Cobb angle) / (2-year Cobb angle) × 100%.
5. Perioperative blood loss (in mL).

6. Total procedure time (from incision to closure) as well as normalized to number of spinal levels from the upper to the lower instrumented vertebra (in min).

7. Accuracy at first attempt: Screws that are not placed and screws that are placed but repositioned after intraoperative verification are noted in the protocol. Accuracy of screw placement will be assessed as a score, calculated as the number of correctly placed screws divided by the total number of screws specified in the protocol (see Appendix 1 in the study protocol). The maximum score is 1, indicating perfect placement according to the preoperative plan. Screws graded Ia or Ib by the Heintel classification [2] are defined as correctly placed. Screws that are not inserted, or that require repositioning after intraoperative verification, will be recorded in the protocol and classified as NOT correctly placed.

8. Intraoperative neurophysiological monitoring. Neurophysiological monitoring is always performed as routine during spinal deformity surgery, with the exception of patients that are non-ambulatory. Motor evoked potential, sensory evoked potential and electromyography data will be collected to investigate any changes in neurophysiological parameters. Any deviations will be noted.

9. Health economics: Total cost per patient during the first 2 years of the study including cost of possible re-admissions and reoperations related to index surgery. Data on costs on the individual level will be collected. These consist of costs for the inpatient and outpatient visits (including surgery, radiographs, navigation), analgesic and antibiotic treatments as well as possible re-admissions related to index surgery.

10. Patient reported outcome measures. Collected from Swespine or similar platforms after 1, 2, 5 and 10 years.
    a. SRS-22r: The SRS-22r is a scoliosis specific questionnaire aiming to estimate quality of life in patients with scoliosis [1]. It contains 24 items divided into 5 domains covering function, pain, self-image, mental health, and satisfaction. An index value is calculated for each domain and a total index value is possible to calculate ranging from 1 (worst) to 5 (best).
    b. EOSQ-24 is a proxy answered questionnaire and will be used in individuals up to the age of 15. It consists of 24 questions of daily function, pain, pulmonary function and mobility [3].
    c. Oswestry Disability index (ODI) is used in individuals from 15 years and older. ODI is a back specific index measuring disability due to back pain [4]. It is the recommended instrument for studies concerning back pain. An index from 0-100 is calculated. An ODI of 0–20 indicate minimal disability, 21–40; moderate disability, 41–60; severe disability, 61–80; severely crippled, 81–100; bed-bound.
    d. EQ-5D 3 level is a generic quality of life instrument and consists of five areas reflecting mobility, self-care, usual activities, pain/discomfort and anxiety/depression [5]. Response aternatives range from no problems to extreme problems. An index can be calculated and depending on baseline value set used the index runs between approximately -0.5 (worst possible health) to 1.0 (best possible health). The EQ-5D-3L will be used for health economic analyses. The EQ-VAS is part of the EQ-5D and registers the patient’s self-rated health on a visual analogue scale (from 0 to 100; best).

e. Postoperative pain relief assessed by NRS at discharge. Additionally, given and prescribed doses of analgesics that follow clinical routine protocols will be registered from the hospital files.

7 STATISTICS

7.1 Sample size calculation

In order to use the win-odds method for a non-inferiority study we performed more than 1000 simulations using the statistical software R. We used the primary variables listed in 6.1 to calculate our sample size and the assumed that the outcomes are independent and that the outcomes were equally distributed among study arms (i.e. we simulated a win-odds of 1.0). We set the power of the study to 80% with a lower limit of confidence interval for win-odds (also called non-inferiority limit) to above 0.60 and calculated a sample size of 150 individuals divided into two treatment arms. We set the possible number of dropouts until the 2-year follow-up to 20%, and the total sample size therefore adjusted to 180 individuals.

7.1.1 What is a non-inferiority limit. The non-inferiority limit is the probability of a patient in the active arm (minimally invasive procedure) to win over a control patient given an evenly distributed number of ties [6].

7.1.2 In the case that the MIS group shows slight benefits compared to the open surgery group then the non-inferiority limit will shift towards 1.0 as the win odds will be greater than 1.0 which was assumed in the sample size simulation.

7.2 Statistical analysis

7.2.1 Primary variables

We selected the above described seven variables in hierarchic order to conduct a win-odds analysis. The variables were selected based on the clinical impact that they have on the patient. The method of win-odds was first introduced as win-ratio [7] in order to analyze composite endpoints based on clinical priorities. The method compares each treatment subject to all controls and the outcome is registered as “win”, “lose” or “tie”. In order to handle large numbers of ties the win-odds was introduced [8] that assigns 50% of the ties to both the numerator and the denominator. Particularly in non-inferiority trials the use of win-odds instead of win-ratio may be more suitable since ties in non-inferiority studies may represent a comparable treatment effect and their number is substantial [6].

7.2.2 Secondary variables

For the secondary variables descriptive statistics will be used to characterize the data; means and 95% confidence intervals will be used for parametric data, medians and interquartile ranges for non-parametric data, and number (proportions) for categorical data. For groups comparisons t-test or ANOVA will be used for parametric distributed data and Wilcoxon, Mann-Whitney or Kruskal-Wallis test will be used for non-parametric distributions respectively, along with post hoc analysis. Categorical data will be compared with Chi-square, McNemar or Sign tests.

Data from the different groups will be compared based on the 'intention to treat' principle. An intention to treat (ITT) analysis means that all patients, regardless of treatment change, loss to follow-up or drop-out, remain in the analysis of the group to which they were randomized. Statistical expertise blinded for treatment allocation will perform the statistical analyses.

8 DATA MANAGEMENT

8.1 Recording of data

Data will be collected from several sources (Table 2). Data primarily collected by Swespine will upon request from the research group be transferred into the study database.

Table 2. *Collection of data.*

Collected by	Swespine/Redcap /Spine Registry	Patient records in each center	Intra- and postoperative imaging
Type of data			
Additional spine surgery	X	X	X
Data on complications and adverse events	X	X	
PROMS	X		
Preoperative planning		X	
Screening question answers	X		
Assessment of radiologically healed fusion			X
Inpatient stay		X	
Total procedure time and blood loss	X		
Health economics		X	
Intraoperative neuromonitoring	X		
Data on planned and actual screw paths		X	X

8.2 Data storage and management

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification. All source data including informed consents, the completed study database, original protocol with amendments and the final report will be stored at the Uppsala University Hospital and Uppsala University for a minimum period of 10 years after termination of the trial.

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and available for data analysis.

9 QUALITY CONTROL AND QUALITY ASSURANCE

The research coordinator will have regular contacts with the research team and participating subjects to confirm that the investigational team is adhering to the protocol. The investigators should ensure that all persons assisting with the trial are adequately informed and trained about the protocol and their trial related duties.

9.1 Audits and inspections

Authorized representatives may perform audits. The investigators must ensure that all study documents are accessible for auditing and inspection. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed and accurately reported according to the protocol, and any applicable regulatory requirements.

10 ETHICS

The study will be performed in accordance with the protocol, with the latest version of the Declaration of Helsinki, and applicable regulatory requirements. The Swedish national Ethical Review Agency will review the study protocol.
The Principal Investigator is responsible for informing the Ethical Review Agency of any amendment to the protocol, in accordance with local requirements.

Informed consent:
The investigators will ensure that the subject is given written information about the nature, purpose and possible risks and benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.
The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.
The original, signed Informed Consent Form (ICF) must be stored at each study site.

Subject data protection:
The Informed Consent Form will incorporate wording that complies with relevant data protection and privacy legislation, and about the collection of data for the purposes of the study.
The Informed Consent Form will explain that study data will be collected from questionnaires, hospital files, images and health databases/registries and will be stored in a computer database, maintaining confidentiality in accordance with national data legislation.

Insurances:
The study subjects are covered by the Swedish Patient Injury Act, and similar in international centers.

11 PROTOCOL DEVIATIONS AND AMENDMENTS

Modifications to the signed protocol are only possible through approved protocol amendments. Details of non-substantial amendments are to be clearly noted in the amended protocol.

In case of a substantial protocol amendment (e.g. change of; main purpose of the trial, primary/secondary variable, measurement of primary variable), the Ethical Review Agency must be informed and should be asked for its opinion/approval prior to implementation of amended protocol, as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The Investigator must not implement any deviation from, or change to the protocol, without discussion with, and agreement by the study group and prior review and documented approval/favorable opinion of the amendment from the Ethical Review Agency, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g. change of telephone numbers).

12 REPORT AND PUBLICATIONS

After completion of the study, the results will be analyzed, and a clinical study report will be prepared. Upon study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results.

13 STUDY TIMETABLE

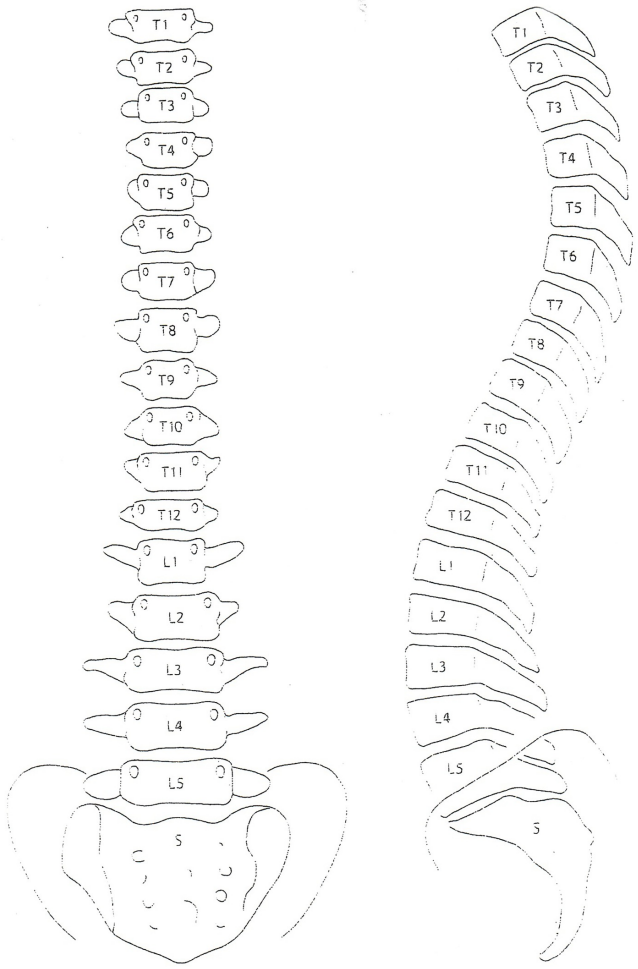
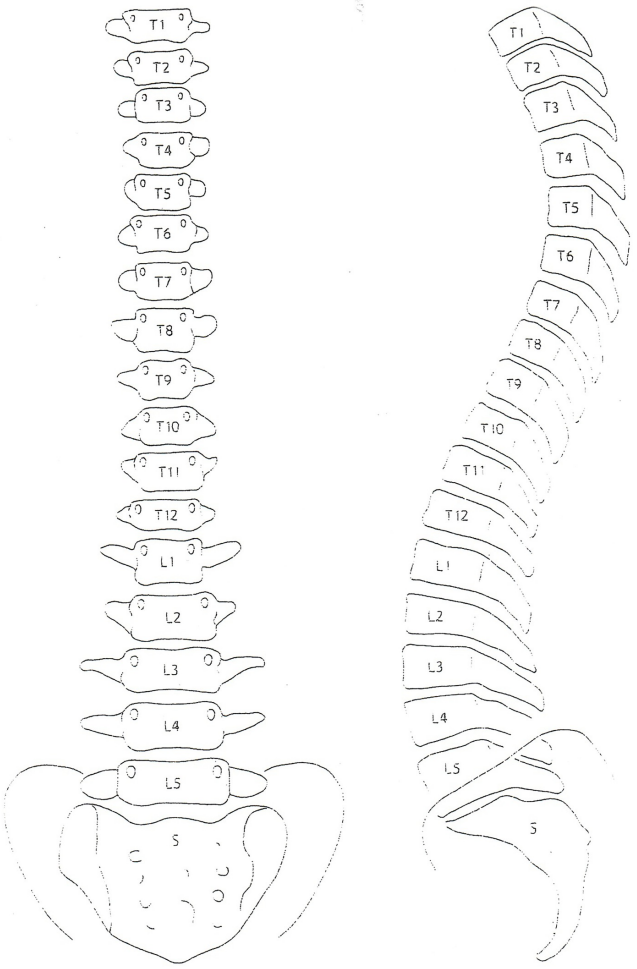
13.1 Study period

Estimated subject enrollment start: mid 2025
Estimated subject enrollment stop: mid 2028
Estimated subject last 2-year follow-up: mid 2030
Estimated study end: mid 2038
Definition of “End of study”
End of study is defined as the last follow-up of the last subject.

14 LIST OF REFERENCES

1. Danielsson, A.J. and K. Romberg, *Reliability and validity of the Swedish version of the Scoliosis Research Society-22 (SRS-22r) patient questionnaire for idiopathic scoliosis.* Spine (Phila Pa 1976), 2013. **38**(21): p. 1875-84.
2. Heintel, T.M., et al., *How safe is minimally invasive pedicle screw placement for treatment of thoracolumbar spine fractures?* Eur Spine J, 2017. **26**(5): p. 1515-1524.
3. Matsumoto, H., et al., *The Final 24-Item Early Onset Scoliosis Questionnaires (EOSQ-24): Validity, Reliability and Responsiveness.* J Pediatr Orthop, 2018. **38**(3): p. 144-151.
4. Fairbank, J.C. and P.B. Pynsent, *The Oswestry Disability Index.* Spine (Phila Pa 1976), 2000. **25**(22): p. 2940-52; discussion 2952.
5. Burstrom, K., M. Johannesson, and F. Diderichsen, *Swedish population health-related quality of life results using the EQ-5D.* Qual Life Res, 2001. **10**(7): p. 621-35.
6. Peng, L., *The use of the win odds in the design of non-inferiority clinical trials.* J Biopharm Stat, 2020. **30**(5): p. 941-946.
7. Pocock, S.J., et al., *The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities.* Eur Heart J, 2012. **33**(2): p. 176-82.
8. Dong, G., et al., *The win ratio: Impact of censoring and follow-up time and use with nonproportional hazards.* Pharm Stat, 2020. **19**(3): p. 168-177.

Appendix 1: Operation protocol MISCOS clinical trial

Preoperative planning	Postoperative outcome
 R L	 R L

Designations

- ✖ Planned screw
- ⊗ Positioned screw according to plan
- ⊘ Repositioned screw
- ⊖ Removed screw
- ○ Not placed screw (not attempted)

Total planned screws……
Total inserted screws……
Repositioned screws……
Removed screws……
Not placed screws……
Procedure time……
Blood loss……
Neurofysiology……
Inpatient stay……