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Indication and treatment of adult spinal deformity
The INTRAKS-study

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Indications and Treatment of Adult Kypho- Scoliosis (INTRAKS Study)

2. Introduction

Background of kyphoscoliosis and its challenges:

Kyphosis is the normal forward rounding of the spine in its double S- shape. Excessive kyphosis can render the spine out of balance. The scoliosis is a sideways curvature of the back. Both adult kyphosis and scoliosis is a common result of degeneration in age. Correction surgery of spine deformities has been done for decades. This type of surgery has been accompanied by complications and variation in outcome and success, therefore, correction surgery of the spine has been reserved as a last resort. Recently, improved surgical techniques for osteotomies and development of equipment has led to a change and increase in indications. There is a need for well conducted studies on this patient group. Therefore, this study aims to evaluate outcome of different treatment options. Some of the reason for the increase in number of patients treated, is an aging population in the industrialized world combined with higher demands for being active at an older age. Patients with kyphoscoliosis disorders that are out of balance, can continue to decompensate, resulting in further nerve-, dura- and spinal cord compression. Suffering from severe pain, paresis and functional deficits, they are not able to participate in the daily life or take care of themselves. The risk for complications by the kyphotic disorder has to be weighed against the benefit of some pain reduction and increased function, even though they face a 30-70% risk of complications, 20-40% of these being major complications that can result in paralysis, bowel- and bladder dysfunction, infections, hardware failure and more [1-8]. These patients already account for large healthcare and social costs. The adult scoliotic disorder can be easier assessed, with less complications, but a combination of kyphosis and scoliosis can also be the case.

Decision making in patient's selection for kyphoscoliosis treatment

Kyphoscoliotic patients have often been through various conservative treatment options in order to strengthen the trunk muscles and often combined with increasing analgesic treatment. In time, conservative treatment might not be sufficient to prevent patients from decompensating and to develop severe back pain and sometimes radicular pain and impaired function. Adult kyphoscoliosis are mostly caused by either primary degeneration, fractures or failure after surgery. Pain and neurological deficits often render patients unable to perform activities necessary for daily living. Additionally, many of these older patients struggle with several comorbidities. These factors in addition to osteoporosis can therefore complicate the surgical planning and treatment.

Future projections predict an increasing older population in industrialized countries and in age osteoporosis is more frequent then in the younger population The incidence of spine fractures due to osteoporosis is significant, resulting in a high number of patients in need of correctional osteotomies [9, 10].

Current indications for surgery by kyphotic disorder is a kyphotic misbalance (widely classified as more than 4 cm off positive sagittal vertical axis (SVA)), regional kyphosis above 20degrees, therapy resistant dorsalgia with radiculopathy and neurological deficits. The scoliotic disorder is often due to degeneration and located in the lumbar, partly in the thoracic spine. A spinal stenosis with a scoliotic disorder and a Cobb angle <20 degrees, can benefit from decompression alone, >20 degrees often needs to be considered for a short or long fixation. Overlooked patients in kyphotic- or scoliotic misbalance undergoing minor spine surgery can have short beneficial effect, but will often soon regain their prior symptoms. A combination of kyphosis and scoliosis is often seen and needs to be addressed although the sagittal condition often is the main problem treating this deformity.

Surgical treatment options

Surgical correction is the only option to improve the balance of the spine by larger angulations and hereby possibly improve clinical outcome. The preferred surgical techniques are anterior release and cage insertion such as Extreme-, Direct- or Oblique lateral interbody fusion (XLIF, DLIF, OLIF) [11] with combined short segment dorsal fixation, as well as Smith Petersen (SP)-/Ponte- and Pedicle subtraction osteotomies (PSO) with multi segmental dorsal fixation [12-15] with or without additional cages in the cases of kyphotic- or kyphoscoliotic disorder. The scoliotic disorders are mostly corrected from a dorsal approach with decompression, Smith Petersen (SP)-/Ponte Osteotomies in multiple levels and long fixation. TLIF, OLIF or XLIF might also address the deformity, the cages in the disc space can aid ventral support and correction in both disorders. Cages provide better stability and might hence reduce screw loosening by kyphosis [14, 16]. In

cases with osteoporosis, cement is often added to the screws or kyphoplasty techniques to the vertebra aiming to improve the fixation. Surgical technique is still a great area of debate. Several articles show a great number of complications such as pseudarthrosis [17-19], proximal junction kyphosis or failure (PJK/PJF) [20-36], neurological complications [37, 38], infection and screw loosening [39, 40]. Osteoporosis in the aging population complicates the treatment and method of surgery further. The consequences of these various surgical techniques are neither fully studied nor understood [41-45]. Another challenge is how to accurately measure and safely perform the desired angulation during surgery.

Adjacent level disease (ALD)

ALD is a common complication after long fixation of the thoracolumbar spine in the adjacent level to the fixation, often resulting in degeneration, spinal stenosis and/or listhesis. Several articles describe the issue, however it is unclear whether ALD is initiated by the rigidity of the fixation or a natural development. If the spinal fixation reaches down to the sacrum (S1), the sacroiliac (SI) joint is the distal adjacent level. The fixation might work as a lever arm causing increased movement or stresses leading to degeneration of the joint. This can lead to pelvic girdle pain [46, 47].

2.1 Needs description:

Following are challenges that still remain to be addressed:

1. Identify predictors for unsatisfactory outcome in adult kyphoscoliosis.

This study aims to create a predictive model for unsatisfactory outcome after deformity surgery in adult kyphoscoliosis. A prospective multicenter observational effectiveness study is constructed to detect a < 30% improvement from baseline in Oswestry Disability Index (ODI) score at 12 months follow up. The predictive model can be a helpful tool in accessing the complexity of this patients and aid in shard decision making and improved surgical planning. Patients are grouped in: 1) unsatisfactory result (UR) < 30% increase from baseline ODI score, 2) satisfactory result (SR) ≥ 30% increase from baseline ODI score. A predictive model will be calculated for both kyphosis and scoliosis together and separately. The same criteria for inclusion are set in the non-surgical group as well as all the data collected, a predictive model will be created if the difference in outcome is significant. The investigators will also look at the patients with a > 10% worsening from baseline in ODI score at 12 months follow up.

2. A prospective multicenter observational effectiveness study of adult kyphoscoliosis treatment, surgical and non-surgical outcome with a 12 months follow up.

a) This part of the study will be looking at the effectiveness of surgery vs non-surgical treatment using the PROMS described in the protocol. It is outcome related, the planned follow up time is 12 months, but the investigators have ethical approval (REK) to continue the data recording for 24 months and more for a sufficient follow up time. It exceeds the time limit for the PhD candidates listed, but others will continue the work. It will contain all the patients included.

b) The subgroups of iatrogenic/degenerative kyphosis and scoliosis will be studied separately as it is known that the mainly scoliotic patients do better than the kyphotic once. Around 30-40 patients will be sufficient in each surgical subgroup, the same in the non-surgical.

3. The kyphotic healed high energy fracture.

One of the subgroups to be investigated is the high energy fractures healed in kyphosis. High energy fractures are typical males in the age of 25-50. The fractures healed in kyphosis with a regional kyphotic angle of >20 degrees and a positive sagittal vertical axis of >4 cm can be included (the rest of the inclusion or exclusion criteria listed will be followed as for the whole study). As this is a subgroup, around 30-40 surgical patients will be sufficient. The investigators hope to have the same number in the non-surgical group to compare with. The main outcome parameter is ODI, but the investigators will also look into the results of the EQ-5D, SRS22 and the numeric rating scale (NRS). As this is a fracture resulting in a secondary deformity, the PROMS listed should be addressing the patient problems.

4. XLIF vs anterior-/transforaminal interbody fusion/pedicle subtraction osteotomy/Smith Petersen/Ponte (ALIF/TLIF/PSO/SP/Ponte).

There is a trend towards using XLIF and OLIF procedures for deformity cases. The investigating party will look into the patients operated using the lateral approaches and compare it towards the dorsal applied interventions (TLIF, PSO, Ponte/SP), if possible also ALIF patients. It should be at least 30-40 patients undergoing the lateral intervention to be able to make a comparison that could be statistical significant.

5. Socioeconomic study; surgery vs non-surgical for adult kyphoscoliosis.

The correctional surgery is often of long duration with expensive implants and highly complicated with high risk of complications. It is costly and the investigators intend to evaluate the socioeconomic burden. The duration of surgery, cost of implants and duration of hospital stay will be registered, the readmission due to complications will be registered for the first 12 months. As EQ-5D is used as a PROM in this study, it will be used for the socioeconomic study.

6. Identify differences in indication, examination and treatment between a European and Asian population.

This is an international multicenter study in cooperation with the Kyoto University Hospital in Japan.

The investigators have already detected some vital differences in the surgical approach for the patient group and further comparison will be of interest. The patients, indications, examination as well as the non-surgical and surgical treatment will be examined.

7. Changes in urination and sexual function in a surgical and non- surgical cohort.

Few studies address this issue, for spine patients it is of great importance and highly underreported. There are few suitable PROMS, so the investigators will use a PROM from a prior study. It is slightly different for men and women due to the differences in sex and it has no scoring system. It has not been validated, so the outcome will be slightly unsatisfactory, the positive sides convinced us to take use of the non-validated form. The investigators have had it translated into Japanese and Swedish and are interested in the Japanese contribution in regard of their cultural differences.

8. Quality control of the Norwegian Quality Register for Spinal Surgery.

The investigators will be conducting x-ray measurements (sagittal vertical axis and pelvic parameters, lumbar lordosis) and compare it with the values that the surgeons have entered into the Norwegian quality register for spinal surgery. The measurements will be conducted by an independent radiologist at Haukeland or Oslo University Hospital in Norway and by the PhD student in Norway. It will be an inter-and intra-observer study. The values mentioned above have been used for the last year in the register and a quality control would be of interest.

9. Spinal stiffness after spinal fusion using the Lumbar spine disability index (LSDI).

The Lumbar spine disability index (LSDI) is developed by our Japanese colleges at the Kyoto University Hospital and they are motivated to test it on the deformity patient. It is the second (2/2) non validated PROMS in this study and have been translated from Japanese to Norwegian and Swedish. It has been published in peer review papers by our Japanese colleges. Most likely it will be of most interest to our Japanese colleges and they will go forward with the publishing of the result.

Hypotheses, aims and objectives

By implementing a retrospective study, we want to look at some baseline characteristics, earlier indications for surgery and complications. This study would involve a mapping of the correctional surgery conducted in both Norway, Sweden and Kyoto (Japan) during the past five years. By establishing this collaboration between Norway, Sweden and Japan, we intend to increase the total number of patients and thereby the impact of our study. In addition, we will conduct a prospective study with additional outcome measures to identify baseline variables, predictors of outcome, benefit of the different treatments. The benefit for the patients will be better total care, we will easier be able to identify patients not to operate, where the risk is too great, develop algorithms to minimized the risks and complications and improve patient outcome. The prospective part includes the same attributes used in the Norwegian registry for spinal surgery. In this way, we can use register data for later quality control. We also plan to use DEXA prior to surgery to assess the correlation of osteoporosis to certain complications such as screw loosening, pseudarthrosis and proximal junction kyphosis/proximal junction failure (PKJ/PKF). The influence on adjacent level disease of different lengths of spinal fixations reaching the sacrum or not is a challenge to detect. Therefore, we want to compare short and long fixation (3 segments or more) and measure the movement in the SI joint with radiostereometric analysis (RSA). Increased movement in the SI joint can lead to degeneration and therapy resistant low back pain requiring further fusion surgery.

<u>Summarized:</u>

- **Firstly,** we want to look at the outcome after surgical and non- surgical treatment of adult kyphoscoliosis, the x- ray measurements and identify predictors for complications among these patients treated with spinal correctional surgery.
- **Secondary** we intend to identify differences in sociodeomographics, indications, examinations and treatments between a European and Asian population.
- **Thirdly** we want to analyze if there is different movement of the SI joint after long and short lumbar fixations.
- **Fourth we want to examine the** socioeconomic burden to society.

3. Project methodology

Study objectives will be addressed in 3 work packages (WP1-3). WP 1 is a retrospective data collection of demographics, clinical and radiological data. WP 2 is a prospective study of demographics, clinical and radiological data. WP 3 is a cohort study measuring movement of the SI Joint with Radiostereometry.

3.1 Project design, method selection and analyses

Work package 1 (WP1) <u>Retrospective analyzes of correction surgery</u>

Patients operated with spinal fixation for the correction of spinal deformity at Oslo University Hospital Ullevål in Oslo Norway, Haukeland University Hospital in Bergen Norway, Malmø Univeritetssjukhus in Sweden, Örebro University Hospital in Sweden and Kyoto University Hospital in Japan, during the past five years. A >1-year retrospective follow-up by questionnaires and radiography.

Inclusion criteria

- ***Main Inclusion: Correction surgery (any technique to achieve balance)***
  - *Fixation 3 levels or more*
    (cage, Smith Petersen/Ponte, Pedicle subtraction osteotomy).
  - *ALIF, XLIF, OLIF, or combinations.*
  - *Corpectomies/VCR.*
- *Minimum criteria:*
  - *Kyphoscoliosis*
    - *Kyphosis >+4cm SVA*
    - ***Or** Scoliosis >30 degree cobb*
- *>25 years.*
- *Past 5 years.*

Exclusion criteria

- Do not want to participate and not able to answer PROMs.
- Acute fractures (not healed fractures).
- Disc prosthesis.

Demographic data

- Age, gender, BMI, mother language, population, race, employment.

Perioperative registration^ (see below)

Questionnaires

- ODI* and EQ 5D**, NRS*** for back pain and leg pain
- Satisfaction of treatment**** and of result***** (explanation asterisk page six)

Conventional Radiography

- X- ray pre- and postoperatively with sagittal vertical axis (SVA), pelvic parameters and radiographic findings of Diffuse idiopathic skeletal hyperostosis (DISH)
- SVA (sagittal vertical axis)

Tabell 1: Outline and time schedule of Work package 1

WP1	Pre OP	Post OP	>12months
Demographics			x
Perioperativ clinical features			x
Prior operativ data			x
Primary correctional surgery			x
Revision of primary surgery			x
PROMS			x
Radiography	x		x

Data collection and registration

Collected from the patient journal:

A: Demographic data (sex, age when operated, Jap/Nor/Swe Nationality, Employment, Education, Profession)

B:Peroperativ clinical features (Smoking, comorbidity, Weight, Height, BMI, ASA, Amount of comorbidities, DEXA).

C:Prior operative data (Times operated before, years ago, indication for prior operation, complications).

D: Primary correctional surgery (date, type of correction, cage, numbers of osteotomy, level of osteotomy, ileum screws used, dorsal fixated levels, anterior and lateral fixated levels, stenosis, adjacent level disease, decompressed levels, scoliosis, kyphosis, BMP used, complications, neuromonitoring, reason for deformation).

E: Revision of primary surgery (time from primary surgery, number of reoperations, type of reoperation, reason for revision surgery, bacteria).

As close to >1 year follow-up after surgery as possible, questionnaires (ODI, EQ5D and Satisfaction of treatment**** and of result*****) is distributed, completed at home by patients, and returned by mail. Patients who do not respond receive one reminder with a new copy of the questionnaires. Patients complete follow-up questionnaires without any assistance from the surgeon. Patient consent is obtained. Degree of correction is assessed pre-operatively and compared to the >12 month follow-up, using conventional x-ray pre- and postoperatively with pelvic parameters and total sagittal spine x-ray for SVA (sagittal vertical axis) and radiographic findings of Diffuse idiopathic skeletal hyperostosis (DISH).

Service for sensitive data (TSD) will be used to transmit data in this part of the study.

Primary outcome measure

ODI at >1 year follow-up

Secondary outcome measures are:

1. EQ-5D at >1 year follow-up.
2. Changes in leg and back pain measured with a NRS at baseline and >1 year follow-up.
3. Satisfaction of treatment and result.
4. Compare surgical procedures.
5. Perioperative complications.

Work package 2 (WP2) <u>Prospective analyses of correction surgery</u>

Patients to be operated for the correction of spinal deformity during the following two-tree years at Oslo University Hospital Ullevål in Norway, Haukeland University Hospital in Bergen Norway, Malmø Univeritetssjukhus in Sweden, Örebro University Hospital in Sweden and Kyoto University Hospital in Japan.

Two studies will be performed. One study comparing patients with a kyphotic deformity after a fracture of the spine with a non-surgical group and one study comparing patients with a kyphoscoliotic deformity (de novo- and idiopathic degenerative scoliosis) and non- surgical treatment. A randomized controlled trial (RCT) will be difficult, so we plan to propensity match the two cohorts and compare correctional surgery and non- surgical treatment at 1 year follow-up.

During the 1 year follow-up period the non-surgical patients will attend an intensive and structured physio-logical training program.

Inclusion criteria

- *>25 years*
- Out of coronar or sagittal balance: A correction of 20 degrees or more is possible due to the degree of degeneration.
- ODI=>30

Exclusion criteria

- Do not want to participate and not able to answer PROMs
- Acute fractures (not healed fractures)
- Disc prosthesis
- Acute fractures
- Neuromuschular cause of deformity (we include Parkinson patients)
- Activ infection or malignancy
- Ideopatic scoliosis with typical add on (we include those that have <20 degrees of scoliosis at Risser 5 and/or the scoliosis increase in age due to degeneration). If unknown, the patient will be included as a de novo scoliosis.

Demographic data

Sex, age when operated, Jap/Nor/Swe Nationality, Employment, Education, Profession Peri- and postoperative registration^ (see below)

Clinical evaluation

- Neurological function lower limbs: Frankel Classification A-E (A=Complete paralysis, B=Sensory only below level of lesion, C=Motor useless, D=Motor useful below level of lesion E=Normal)
- Bladder- and sexual dysfunction

Questionnaires

- ODI* and EQ 5D**, NRS*** for back and leg pain, LSDI******, SRS 22r*******

Radiography:

- Conventional full length, standing x-ray from C2- femoral heads with hips and knees extended, shoulders and elbows flexed with finger tips placed on the clavicle, pre- and postoperatively with:
    - pelvic parameters (3 and 12 months po).
    - SVA (sagittal vertical axis), TK (thoracic kyphosis), (3 and 12 months po)
    - Central sacral vertical line (CSVL) to the right or left in mm/coronar balance
    - Lateral translation of L3 and L4 to the right or left in mm
    - Lumbar olisthesis in mm
    - DISH
    - Hip flexion
- MRI preoperative; Schizas grading of spinal stenosis (A-D), Lee grading of foraminal stenosis (1-3).
- CT pre- and postoperative (1 and 2 years postoperative; determine fusion after surgery).

DEXA of the hip and spine before operation to verify possible osteoporosis

Tabell 2: Outline and time schedule of Work package 2

WP2	Pre- op	OP	Post- op	3 months	12 months
Demographic data		x			
Perioperativ clinical features		x			
Prior operativ data	x				
Primary correctional surgery		x			
Revision of primary surgery					x
ODI	x				x
EQ5D	x				x
NRS	x				x
SRS 22r	x				x
LSDI					x
DEXA	x				
Neurological function	x				x
Radiology	x			x	x

Data collection and registration

On admission for surgery, patient consent is to be obtained. The patient complete the demographic data - and baseline questionnaire (ODI, EQ5D, NRS, SRS 22r) and will be examined for function of the lower limbs using the Frankel classification and hypoesthesia is recorded on with side and dermatome on a scale from 0-3 (0=no numbness, 1=inconsistent numbness, 2=consistent numb with some feeling, 3=complete consistent numbness). The MRI findings are classified using the Schizas- and Lee Classifications according to side and level.

During the hospital stay, the principal investigator at each site records:

A:Peroperativ clinical features (Smoking, comorbidity, Weight, Height, BMI, ASA, Amount of comorbidities).

C:Prior operative data (Times operated before, years ago, indication for prior operation, complications)

D: Primary correctional surgery (date, type of correction, cage, numbers of osteotomy, level of osteotomy, ileum screws used, dorsal fixated levels, augmented screws, percutaneous, anterior and lateral fixated levels, blood loss, stenosis, adjacent level disease, decompressed levels, scoliosis, kyphosis, BMP used, Type of bone graft, complications, neuromonitoring, reason for deformity, duration of surgery, duration of hospital stay).

E: Revision of primary surgery (time from primary surgery, number of reoperations, type of reoperation, reason for revision surgery, bacteria).

A questionnaire is distributed at the 12-month follow-up after surgery, completed by the patient and returned to the coordinator The coordinator will give aid if necessary. Patients who do not respond will be contacted and receive one reminder with a new copy of the questionnaire. Patients complete preoperative questionnaire data and postal follow-up questionnaires without any assistance from the surgeon. At the same time the patient will be examined clinically (Frankel and numbness scale) at the follow up control.

Degree of correction is assessed pre-operatively and compared to the 1 year follow-up, using conventional x-ray pre- and postoperatively with pelvic parameters and total sagittal spine x-ray for SVA (sagittal vertical axis).

A CT scan is performed at 1 and 2 years after surgery to investigate degree of fusion.

DEXA of the proximal femur and lumbar spine to determine T-score and evaluate degree of osteoporosis prior to surgery.

A: Osteopenia (T-score between (-1 and -2,5): 800 IE Vit. D and 1000mg Calcium a day)

B: Osteoporosis (T-score <=-2,5): Aclasta/Alendronat 70mg/week or Zolendronat iv/x1 year, combined with Vit. D and Calcium)
C In other severe cases with kidney dysfunction or no effect of Bisphosphonat treatment, Prolia/Denosumab or Forsteo/Teriparatid/PTH-analog can be the treatment of choice.
Conservative treatment: A homepage will be developed in English, Japanese and Norwegian, with specific videos containing training instruction for treatment after surgery, developed with dedicated physiotherapists from Rikshospitalet, Oslo.
RSA (Radiostereometric Analysis) of the SI joint, see work package 3.

Primary outcome measure

ODI at 1 year follow-up.

Secondary outcome measures

1. Changes in HRQL measured with the EQ-5D between baseline and 12-month follow-up.
2. Changes in leg pain and back pain measured with NRS between baseline and 12-month follow up.
3. Changes in subjective domains measured with SRS 22r between baseline and baseline and 12-month follow up.
4. Economic, cost effectiveness.
5. Surgical procedures involving PSO (pedicle subtraction osteotomy), IPO (interpedicular osteotomy), cage or not, levels fixed, duration of operation and hospital stay.
6. Perioperative complications.
7. Lumbar stiffness disability index (LSDI).

Additional follow up at 2, 5 and 10 years with PROMS and x-ray will follow.

Work package 3 (WP3) <u>Movement of the SI joint after different lumbar fixation</u>

To evaluate the influence of different surgical treatment options for kyphoscoliosis we measure the movement of the SI joint with Radiostereometric analysis (RSA) after lumbar fixation.

Inclusion criteria

- Long fixations of 3 or more segments down to S1, (also including not correction surgery patients).
- One segment fixations in the level of L4/5 regardless of olisthesis.

Exclusion criteria

- Medical conditions that affect the SI joint (Sacroileitis, Ankylosing spondylitis, psoriasis, autoimmune illness)
- Do not want to participate and not able to answer PROMs
- Iliac screws

RSA is a high precision *in vivo* measuring method for motion. We intend to measure sacroiliac joint (SI) movement in long fixations compared to short fixations. The Center for Implant and Radiostereometric Research Oslo has extensive experience with RSA and established state of the art measuring method of movement in the SI joint [48].
At Oslo university hospital tantulum markers are inserted during spinal surgery into the SI joint. We select patients scheduled for 2 types of surgery:

- Short lumbar fixations (one segment)
- Long fixations down to S1 that include three or more segments in the cranial direction.

We will measure the movement in the SI joint at 12 months after the operation and compare it to the postoperative status in the two groups.
In the 10 first patients we will also do a low dose CT with and without provocation to compare the RSA method with the Sectra Implant Movement analysis using the low dose CT. If the methods are equivalent, we can proceed with the CT method for the remaining 20 patients.

Questionnaires

- ODI* and EQ 5D**, NRS*** for back and leg pain
- Satisfaction of treatment**** and result***** (explanation asterisk page six)

Null hypothesis

- The SI movement will not increase because of long fixation down to sacrum, the SI joint will not work as an adjacent level and not compensatory increase the movement.

- The increased movement will not result in low back pain and /or pseudo radicular pain to the lower limbs.

Explanation to the Questionnaires for the Work packages 1-3

- *ODI is one of the principal condition-specific outcome measures for of spinal disorders.
- ** EQ-5D is a generic and preference-weighted measure of HRQL.We use 3L.
- *** Patients report leg pain and back on a numeric rating scale from 0 to10=maximum pain.
- ****Satisfaction of treatment on a five point Likert scale.
- *****Satisfaction of result of the treatment seven point Likert scale.
- ****** Lumbar stiffness disability index, questions regarding stiffness after lumbar fusion surgery.
- *******SRS 22r contains the subjective domains; pain, self-image, function/activity, mental health, satisfaction with management.

Statistical analyzes

WP1: Categorical variables will be analyzed by Chi-square, ordinal data by non-parametric methods and normally distributed scaled data by parametric methods. Multiple logistic regression will be used for predictor analysis (WP1). The centers operate approximately 15 -20 patients annually. This results in around 150 - 200 patients in the retrospective cohort after a study period of 5 years.

WP2: Altogether 75-100 patients are expected eligible for inclusion in the surgical group of WP2 annually. For non-surgical treatment, approximately the same number. By using alfa=5% and power=80% to detect 30% ODI improvement from baseline and 30% improvement in proportion of patients that improved and calculating for 10% crossover, 10% mismatch in the propensity score matching and sufficient power for the subgroup analyzes, we will need a total of 300 patients. Considering drop outs, we would have enough patients after 2-3 years of inclusion.

Predictive analysis: Frequency analyses for categorical variables will be conducted via Pearson's c2 analysis. All analysis will be conducted using commercially available software (SPSS version 24, IBM Inc.) and the level of significance is set to $p<0.05$ in a two-sided test. For the predictive model, missing values within the database will be imputed using standard techniques such as mean and median imputation. Once a complete data set is constructed, an ensemble of decision trees will be constructed with a binary target variable that includes patients with: 1) unsatisfactory result (UR) < 30% increase from baseline ODI score (code = 0), 2) satisfactory result (SR) ≥ 30% increase from baseline ODI score (code = 1). The decision-tree algorithm is C5.0 and 5 different bootstrapped models will be built. Internal validation is accomplished via a 70/30 data split for training and testing the model, respectively. Final overall predictions from the models will be combined and chosen by voting with random selection for tied votes. Overall accuracy and the area under the receiver operating characteristic (AUROC) curve will be calculated as well as predictor importance as determined by the model. The model will be built using commercially available software (SPSS Modeler version 24, IBM Inc.).

A sensitivity analysis will be performed 1-2 years into the study period, the MCID/"satisfactory result" and power will be adjusted accordingly.

WP3: RSA is a high accuracy measuring method. With a precision of 1 degree for rotation we need 10 patients in each group to detect a difference of 2 degrees for power of 90% on an alpha = 99% confidence level. Taking drop-outs into account we need a group size of 15 resulting in 30 patients for WP3 (Two- sided T-test).

4.2 Participants, organization and collaborations

Project management

Two levels of management have been defined, the coordination level and the operational level, to ensure a management structure which provides full transparency and control of the entire project in terms of time, resources and cost monitoring and which is able to react flexibly to all new insights in the course of a research project. The activities at the coordinating level will focus on the overall management of the study, including administrative and financial aspects and monitoring progress and activities and will also keep an open dialogue with the patient representative during the study (NorCRIN). The objective of the operational level is the provision of an effective and successful operational workflow, during which the Principal Investigators (PI) at the collaborating centers in Oslo, Bergen, Sweden and Japan will coordinate the WP1 and WP2 which involve proper data collection, storage and transmission.

Organization and collaboration

The applicant is the PhD candidate, and the project owner is Haukeland University Hospital (HUS), Bergen. The departments/institutions present in this study have an active research fellowship embracing multiple research groups and publications. We have extensive experience in coordinating and conducting large longitudinal multicenter trials.

Project leader and responsible institution

Stephan M. Röhrl, PhD, MD, Ass. Professor, Head of Center for Implant and Radiostereometric Research Oslo, President of Knee and Hip Register, Oslo University Hospital, Oslo, Norway.

Supervisors

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Collaborating partners

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Takayoshi Shimizu, Ass. Professor, PhD, MD, Kyoto University Hospital, Kyoto, Japan

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Gauti Freyr Sigmundsson, MD, PhD, Head of Department Örebro University Hospital.

Thomas Kibsgård, Ass. Professor, PhD, MD, President Pelvic Girdle Pain Society, Head of Department Rikshospitalet, Oslo, OUS.

PhD candidates

Vinjar Myklevoll, MD, Haukeland University Hospital, Bergen.

Norimasa Ikeda, MD, Kyoto University Hospital, Kyoto, Japan.

We have collaboration partners and coordinators in each health region as well as Malmø, Sweden and Kyoto, Japan. Our research group also has collaborative relationships with research groups from Sweden, Denmark and the Netherlands. The collaboration between our countries will help to develop new ideas within the field, while also increasing patient numbers and work force. In addition, the unique Swedish and Norwegian National Quality Registers for Spinal Surgery, will make it possible to construct a common knowledge platform in order to generate a streamline treatment algorithm for this severely debilitated patient cohort. This Registers is also vital in compiling data for expert studies addressing the complications related to adjacent level disease of the SI joint [41-45, 48, 49]. CIRRO is a research group located at the Oslo University Hospital and has conducted research within the field of bone and implant research by implementing mainly RSA and DEXA analysis. Thomas Kibsgård at Rikshospitalet has earlier conducted extensive research on the SI joint with RSA and has experience within this area. The project leader Stephan Röhrl is the main supervisor for the PhD candidate.

4.3 Budget

The budget is specified in the application form.

4.4 Plan for activities, visibilities and dissemination

The planned study period is 6 years (50% research position). The progress of the work packages will be monitored with the help of defined milestones (see electronic form). Dissemination activities will be organized in close collaboration with patient representatives, and will be a regular activity throughout the course of the project. Internal dissemination, will be conducted with the objective of strengthening and reinforcing collaboration through internal newsletters distributed every 6 months to collaborating partners. In addition, there will be project meetings allowing a platform for open discussion among all operating levels. Communication among the research consortium will be ensured. External communication activity will disseminate the results and the impact of the study with all relevant stakeholders; healthcare providers, the scientific community, patients and patient organizations. These measures will be achieved by participation in conferences, production of posters, publication of patient-friendly information booklets and proactively informing media outlets and patient organizations. Scientific results from the project will have the potential to be published

in a high impact journal like BMJ as well as field specific journals such as Spine and Eurospine.

4.5 Plan for implementation

The experience from the present project is expected to form the basis for future national patient loops and diagnostic work-up schemes for patients with kyphoscoliosis, within 3-4 years after project start. It will be presented at national and international orthopedic meetings, and information will reach out to the spine associations in the respected countries about project result and implementation for treatment. We intend to summarize our information in clinical recommendations that will be disseminated trough the report of the Swedish and Norwegian spine registry and the clinical orthopedic handbook of associated hospitals, both freely available online. Original research articles will be published in peer review journals. We establish a direct dialog with regional scoliosis association (user involvement), which will assist to inform its members on a national level. We will summarize the results in a short film on YouTube to reach out to patients searching the internet for information about kyphoscoliosis.

5. User involvement

A patient representative which has been involved with spinal surgery as a patient herself. Her role within the study will to be an active, contributing member of the project team whose role involves both discussion and observation throughout the study. In addition to collaborating with the patient representative throughout the study progression we will specifically seek feedback regarding prioritization on the reporting upon relevant outcomes and eventually the dissemination of results. Platforms for discussion and observation will be made including telephone conferences, meetings and free dialog between all partners involved. To optimize collaboration between all parties, mutual expectations will be agreed upon at the project's start, particularly regarding expected participation and role, time investment, reimbursement and acknowledgement. A confidentiality form will be employed ensuring the protection of unforeseen events within the progression of the study, discussion of project participants along with consideration regarding confidentiality of pre-reviewed results before dissemination.

6. Ethical perspectives

The studies will be conducted in accordance with the declaration of Helsinki II. All participants provided written informed consent. Ethical approval is applied for at the Norwegian Regional Ethics Committee (REK nord) with the references 2017-13778, 13779 and 13780. All personal information and data will be handled in accordance with appropriate guidelines, and will be stored anonymously. Each patient receives a study ID. The randomization key and identity is stored separately.

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