CLINICAL STUDY PROTOCOL

SunBurst- StUdy oN Burst fractures

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SYNOPSIS

Title: SunBurst- StUdy oN Burst fractures

Rational for conducting the study: Treatment for thoracolumbar burst fractures ranges from no treatment to operative treatment. Current treatment evidence is based on retrospective or observational studies and a few small randomized controlled trials. The aim of this study is to compare operative versus non-operative treatment for thoracolumbar burst fractures.

Study design: Randomized controlled clinical trial

Study population: Individuals aged 18 through 66 years

Number of individuals: 202

Inclusion criteria:
• Written informed consent
• Age 18 through 66 years
• Single level thoracolumbar burst fracture

Exclusion criteria:
• Neurological injury of the spinal cord or cauda equina
• Definite rupture of the posterior tension band
• Anchylosing spinal disorder spanning the fracture area

Primary outcome variable:
The primary outcome will be Oswestry Disability Index, a measure of back function at 1 year.

Study period: Sep 1st 2021-Dec 31st 2036 (estimated)

SIGNATURE PAGE

I confirm that I have read and understood this protocol and that I will work according to the protocol. By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, and local regulations governing the conduct of clinical studies.

2023-01-19

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
rRCT	Register-based Randomized Controlled Trial
SFR	Swedish Fracture Register
NPR	National Patient Register
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
ODI	Oswestry Disability Index
SMFA	Short Musculoskeletal Function Assessment
EQ-5D-5L	EQ-5D five level

1. INTRODUCTION

1.1. Background

The overall purpose is to improve treatment of thoracolumbar fractures. Thoracolumbar fractures are common and occur at all ages. A thoracolumbar fracture has a large impact on the individual and may be associated with long time disability.

Most of the spine fractures occur in the thoracolumbar region, usually defined as the region between the tenth through the second or third lumbar vertebra. This region is more prone to injuries since it is the interface between the stiffer thorax and the mobile lumbar spine (Denis 1983).

We will use the newly developed Swedish Fracture Register (SFR) as a basis for this first ever nationwide register based randomized controlled trial on vertebral fractures. The results may be immediately implemented and treatment optimized. In Norway, the same information will be collected from questionnaires, medical records, and a secure web application.

1.2. Rationale for conducting this study

Current treatment evidence is based on retrospective or observational studies and a few small randomized controlled trials. The randomized controlled trial in this project can delineate the treatment efficacy of operative and non-operative treatment for thoracolumbar burst fractures. Also, it helps allocating money to interventions that do the most good.

Reasons for surgical treatment include fast mobilization and return to normal activities, prevention of spinal deformity development, or the development of neurological problems (Rajasekaran 2010). Over the years most of the treatment studies of thoracolumbar fractures have been retrospective. Only a few randomized trials exist (Abudou, Chen et al. 2013, Wallace, McHugh et al. 2019). Thoracolumbar burst fractures that account for around 45% of the thoracolumbar injuries is one of the areas of most controversy. For thoracolumbar burst fractures, a meta-analysis of the only two existing randomized trials found no advantage for surgery over brace treatment , and a meta-analysis of another two randomized trials found no advantage of brace treatment over no brace treatment (Wallace, McHugh et al. 2019). All the existing trials suffer from few participants. In meta-analyses, 87 individuals have been randomized to surgery or brace (Abudou, Chen et al. 2013), and 119 individuals have been randomized to either brace or no brace (Wallace, McHugh et al. 2019). A recent search for the writing of the current application has not revealed any new published studies with high level of evidence.

A search of *ongoing* clinical trials revealed the following two studies. An observational study on burst fracture with or without suspected posterior ligamentous injury treated with or without surgery with 208 planned participants (https://clinicaltrials.gov/ct2/show/NCT02827214). A randomized study will compare brace and no brace in individuals with thoracolumbar burst and compression fractures with 200 planned participants (https://clinicaltrials.gov/ct2/show/NCT03952182).

Due to the relatively scarcity of evidence a current practice variation is evident, ranging from surgery to brace to no treatment other than analgesics within Sweden (2017), as well as

worldwide. No evidence exists on the cost-effectiveness of the intervention under consideration. Health economic analyses are important to improve allocation of scarce healthcare resources and have the potential of decreasing waste.

1.3. Ethical issues

We think it is important to evaluate the effect of surgical compared to non-surgical management in thoracolumbar burst fractures. Both non-surgical and surgical care are available today and routine care. The current situation with scarcity of evidence leads to a practice variation, ranging from surgery to brace to no treatment other than analgesics. We do not know whether unnecessary surgery is performed, which could possibly be associated with complications, or the opposite, if surgery should be offered frequently and result in a faster return to activity and maybe fewer complications than non-surgical management. Although this study require that 50% of the randomized study subjects go through surgery with the potential risk this entails (e.g. general anesthesia, infection and bleeding), surgery is not an uncommon practice today. However, non-surgical management is also common. A failed non-surgical management may result in later need for surgery, which possibly result in poorer outcome and longer sick leave. We expect that this adequately powered study could answer the research questions and that the results measure up in relation to the ethical issues and the uncertainty of best care today.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary objective

1) The primary objective is to compare patient-reported outcome for two common treatments for thoracolumbar burst fractures, surgical stabilization and non-surgical care. Patient-reported outcome is primarily assessed with the back-specific patient-reported outcome questionnaire, Oswestry Disability Index (Fairbank and Pynsent 2000).

2.2. Secondary objectives

The secondary objectives of this study are to evaluate whether:

2) surgical stabilization result in shorter time to return to work,
3) surgical stabilization result in fewer collected doses of analgesics (opiods and non-opioids) compared to non-surgical care,
4) surgical care result in fewer adverse events than non-surgical care,
5) surgical care is cost effective as compared to non-surgical care,
6) the associated cost is different between treatment arms, both in aggregate or by its components (both direct healthcare costs and indirect costs e.g. sick leave),
7) radiographs are needed to monitor non-surgical treatment and surgical treatment outcome of thoracolumbar burst fractures,
8) patients with thoracolumbar burst fractures included in a randomized controlled trial have the same outcomes as patients in an observational study with identical inclusion criteria.

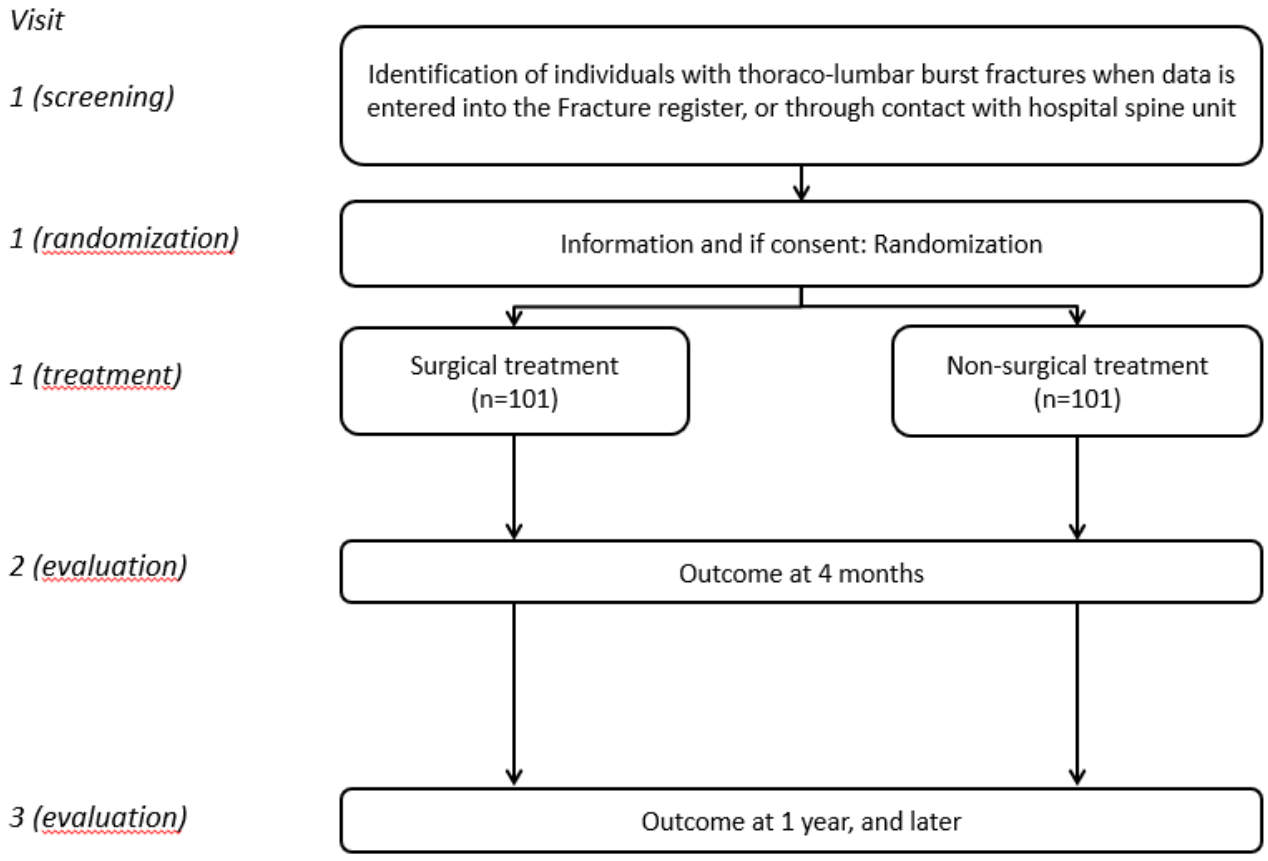
3. STUDY DESIGN AND PROCEDURES

3.1. Overall study design and flow chart

This is an international, multicenter open label parallel assignment randomized controlled trial (RCT) (Figure 1). The trial will use a pragmatic approach. The Swedish centers will use the SFR

infrastructure and other existing databases for outcome assessments, making this a register-based RCT (rRCT) for the Swedish part of the study (Wennergren, Ekholm et al. 2015, Morgonskold, Warkander et al. 2019). Due to the nature of the study, comparing a surgical and a non-surgical treatment alternative, an open approach is the most feasible design. Blinding of the patients and health care personnel will not be done. Patient-reported outcomes will however be assessed without influence of the care giver.
Based on earlier studies and data from the SFR we estimate that 250 individuals yearly are treated for thoracolumbar burst fractures in Sweden and could be eligible for the RCT. Our time plan includes study start (mid 2021), last patient included (2025) and last 1-year follow-up (2026). Registry outcome data, and similar data collected from questionnaires and medical records in Norway, are planned to be collected at 5 and 10 years. The study may have come to an end 2036. However, delays in similar studies are not uncommon.

Figure 1. *Study design randomized controlled trial.*



3.2. Rationale for study design

The rRCT study design in Sweden enables us to perform a national multicenter randomized controlled trial with a large sample size. Primary outcome is based on patient-reported outcome which will be collected on paper and through the SFR platform. In addition, important outcomes will be retrieved from health data registers and radiographic images. The Swedish personal identity

number (PIN) allows the investigator to cross-check registers on an individual level. Data on fracture classification, age, sex, type of trauma, time of diagnosis and time of treatment will be collected in the SFR. The study may be expanded internationally by collecting similar data from questionnaires, medical records, by secure web application. In Norway, the same data will be collected and processed using questionnaires, medical records, and the secure web application RedCap. Delabeled radiographic images will be sent using password-protected and encrypted hard disk drives.

Randomization in Sweden will be done within the SFR registry-platform after informed consent has been obtained from the patient. In Norway, randomization will be done using the web application RedCap. Further variables will be registered by cross-checking with the National Board of Health and Welfare (National Patient Register, Swedish Prescribed Drug Register), Swedish Social Insurance Agency (Försäkringskassan) and Statistics Sweden. Mortality is automatically cross-checked with the Swedish Cause of Death Register and available in the SFR. The same variables will be collected from questionnaires and medical records in Norway.

3.3. Study visits

Patients will be assessed at the time of fracture, at about 4 months, and 1 year (Figure 1, Table 1). There will be one formal clinical follow-up visit in addition to the local clinical routines, at 1 year. Additional follow-ups at 5 and 10 years through registry data in Sweden and from questionnaires and medical records in Norway are planned. We do not exclude the possibility that patients will be asked to provide patient-reported outcomes also at these time points. To minimize data loss reminders for patient-reported outcome data will be made (Table 1).

Table 1. *Study activities.*

Day:	Visit 1 Screening and randomization *Initial visit*	Visit 2 *3-4 months*	Visit 3 *1 year*	*5 years*	*10 years*
Informed consent	X				
Demography	X				
Inclusion/exclusion criteria	X				
Randomization	X				
Patient-reported outcome data	X*[a]	X** [a]	X* [a]	(X** [a])	(X** [a])
Imaging	CT/MRI	CT	CT/MRI/standing spine radiograph		
Registry data	X	X	X	X	X

*ODI collected on paper. SMFA and EQ-5D-5L are collected through the SFR platform. All patient-reported outcomes are collected from questionnaires and medical records in Norway.

**ODI, SMFA, EQ-5D-5L collected on paper

[a] If patient-reported outcome measure (PROM) data is not captured as planned reminders on paper or telephone will be made. It is possible to capture all PROM data by telephone if paper or web-based collection does not work (Martin, Yaszemski et al. 2019). A specific telephone interview version of EQ-5D-5L is available. For SMFA and ODI the standard questionnaire will be used.

4. STUDY POPULATION

4.1. Inclusion criteria

- Age 18 to 66 years
- Patients with a single level burst fracture type A3 or A4 between thoracic vertebra (T10) and lumbar vertebra 3 (L3) (Figure 2) (Reinhold, Audigé et al. 2013).

  Individuals with co-existing fractures in same level pedicles and same level or adjacent level posterior structures (lamina, transverse processes and/or spinous processes) are eligible for study inclusion if the posterior tension band is determined patent or indeterminate.

  Individuals with minor fractures in adjacent vertebra/es (minor avulsions of the vertebral body, lamina, transverse processes, spinous processes) are eligible for study inclusion as long as these minor fractures in themselves would not have resulted in any treatment.

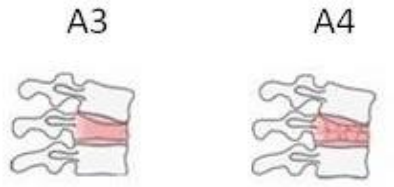
  Individuals with vertebral body or posterior structure edema seen on magnetic resonance imaging (MRI) outside the computer tomography (CT) defined fracture area are eligible for study inclusion.

  Individuals with kyphosis in the fracture are eligible for study inclusion if the posterior ligamentous structures are patent or indeterminate (as determined on MRI).

  Patients with single level root compromise of minor importance are eligible for study inclusion.

- Consent for study participation.

Figure 2. *Drawings from the Swedish Fracture Register of type A3 and A4 burst fractures. Fracture type A3 is a burst fracture involving one endplate and the posterior wall of the vertebral body. Fracture type A4 is a burst fracture involving both endplates and the posterior wall of the vertebral body.*



4.2. Exclusion criteria

- Unable to consent, no consent given, or not informed.
- Individuals with neurological injury involving more than a single level root, i.e. spinal cord and/or cauda equina injury are excluded.
- Individuals with definite rupture of the posterior tension band (through bony and/or ligamentous structures) are excluded.
- Individuals with anchylosing spinal disorders spanning the fracture area are excluded.
- Individuals not deemed suitable for operative or non-operative treatment due to co-morbidities are excluded.
- *Examples of such co-morbidities is established osteoporosis that would impair the possibility to maintain integrity of spinal implants, pathological fractures, severe cardiac or pulmonary* compromise, or other systemic disease that would result in such high anesthesiologic risk that surgery would not be attempted.
- Individuals already included in the study cannot be randomized again if they get an additional spine fracture.

4.3. Subject enrollment and randomization

When data for the fractured individual is entered by the treating physician in close connection to the fracture event in the SFR, a message will appear on the screen if the individual fulfills the inclusion criteria.

The treating physician is instructed to contact the closest university hospital (all have 24-hour spine surgery service) to cross-check the inclusion criteria before randomization.

In the event that a patient is not entered into the SFR by the treating physician, it is our experience that the university hospitals on call spine surgery services is often contacted to discuss treatment and eligible patients are thereby identified. All Swedish university hospitals and county hospitals that perform surgery on spine fractures are involved in the study.

In Norway, the site investigators will screen patients for eligibility using RedCap. Subject eligibility will be established in the SFR for Swedish patients and in RedCap for Norwegian patients before treatment randomization. The study information and consent form can be printed from the SFR website or the RedCap website. Subjects will be randomized strictly sequentially, 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.

Randomization procedure

Randomization will be performed through the Spine service at one of the participating hospitals. To enter the randomization module on the SFR website in Sweden, patient and fracture data already entered by the non-university hospital must be deleted, and be replaced by data entered into the university hospital SFR website. In Norway randomization will be performed in RedCap after the screening questions have been answered.

Mistakenly randomized individuals

In the event that an individual does not fulfill the inclusion criteria and was mistakenly randomized, the central study coordinator and steering committee must be informed by the participating clinic. The event will be noted in the study log book. The randomized individual will not be replaced by another in 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. Patients prematurely withdrawn from the study will not be replaced.

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

The patient can be screened for study inclusion again, by the SFR online screening module in Sweden or by RedCap in Norway, if no active treatment, such as surgery or brace treatment, has been initiated.

5. STUDY TREATMENTS

5.1. Surgical treatment

Surgical stabilization is performed. The recommended surgical procedure is posterior fixation with either open or minimally invasive approach. Based on the available evidence, pedicle screw should be inserted one level above and below the fractured vertebra, without fusion or decompression (Chi, Eichholz et al. 2019). If feasible, pedicle screws are inserted also in the fractured vertebra. However, the study is pragmatical and the choice of surgical procedure and numbers of vertebrae fixated will be at the discretion of the surgeon. The choice of supplier and brand of implants are

based on the established practice at of each participating center. Brace treatment will not be used postoperative. Early ambulation after surgery is encouraged. Surgery is to be performed within 2 weeks from the injury. Physiotherapy and other measures of rehabilitation are prescribed on an individual basis. Additional surgery for removal of implants is optional and can be done according to local routines.

5.2. Non-surgical treatment

No surgical stabilization is performed. Early ambulation after treatment randomization is encouraged. Evidence for an effect of brace treatment on pain, disability and kyphosis on less severe thoracolumbar burst fractures (type A3) is lacking, but only based on two small studies (Wallace, McHugh et al. 2019). Data on the effect of brace versus no brace in the more severe burst fractures (type A4) is missing. The research group's clinical experience of patients with more severe burst fractures (type A4) is a possible role of a brace in the short term treatment of pain. Therefore, brace treatment may be offered up to 3 months for pain relief. The brace is a standard three-point hyperextension brace which is fairly comfortable to use. The choice of supplier and brand of brace are based on the preference of each participating center. The brace will only be used upon mobilization. Brace use will be estimated by the patient at the 3-4 month follow-up, but time in brace may possibly be estimated by a temperature timing device (to be decided). Physiotherapy and other measures of rehabilitation are prescribed on an individual basis.

5.3. Blinding

The study design comparing a surgical to a non-surgical treatment does not allow blinding. Patient-reported outcomes will however be assessed without influence of the care giver.

5.4. Randomization

Randomization will be performed by the web-based platform of the Swedish Fracture Register in Sweden and by the web application RedCap in Norway using an allocation sequence hidden from the healthcare personnel and provided by a statistician at Uppsala Clinical Research Center and independent from the study. Sweden and Norway will have separate allocation sequences. The subjects are randomized in a 1:1 ratio, without stratification.

5.4.1. Platform problems inflicting screening and randomization

Platform problems are expected to be few and of short duration. Screening and randomization will in such cases be postponed until the platform is in working order again.

5.4.2. Treatment cross-over control group

In case of the uncommon event of neurological compromise after inclusion in the study (Rajasekaran 2010), the reason for this has to be assessed. If this is due to canal compromise or progressing kyphosis, surgery may be advisable. Inability to initiate mobilization in a patient due to intense pain despite adequate analgesics and possibly a brace, may be a reason to resort to surgical treatment. A change in treatment will be documented in the Swedish Fracture Register in Sweden or in RedCap in Norway.
An increasing kyphosis at follow ups is not a reason for treatment change since no evident relation between kyphosis and patient-reported outcome has been described (Rajasekaran 2010). Initial

extent of canal compromise or an increase in canal compromise during follow-up is not a reason for treatment change in the absence of neurological symptoms (Rajasekaran 2010).

5.5. Concomitant medication

Patient will receive their ordinary medications and the standard pre- and postoperative treatment at each participating center.

6. STUDY MEASUREMENTS AND VARIABLES

6.1. Primary variable

- The primary variable/outcome of this RCT is Oswestry Disability Index (ODI) score 1 year after the fracture. ODI is a back specific index measuring disability due to back pain (Fairbank and Pynsent 2000). It is the recommended instrument for studies concerning back pain. It consists of 10 questions with six answer alternatives (from no problems to severe problems) on different aspects of back function and 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. We assume that individuals before the fracture have ODI on par with population-based data. At best, ODI after thoracolumbar fracture treatment approaches prefracture levels. Population-based data indicate a mean ODI of 8 for adults (Tonosu, Takeshita et al. 2012, Endler, Ekman et al. 2019).

  ODI data after thoracolumbar fracture are scarce. Mean ODI was 36 two years after surgical treatment of thoracolumbar fractures in one study (Wei, Liu et al. 2010) . In Swespine, mean ODI was 22 one year after surgical treatment (unpublished data). In 27 non-surgically treated individuals mean ODI was 11 two decades or more after a burst fracture (Moller, Hasserius et al. 2007) .

  ODI is not part of the SFR and will be collected by paper in Sweden and Norway (Table 1). To minimize data loss reminders for patient-reported outcome data will be made (Table 1) (Martin, Yaszemski et al. 2019). The primary endpoints will be 1 year after the patient has been randomized. Data from other registries in Sweden will be collected retrospectively.

  If one question is left blank or missed, the ODI score is calculated as the percentage of the answered questions. If more than one box is marked for a question, the highest value will be counted (Fairbank and Pynsent 2000).

6.2. Secondary variables

See also 2.2 above. In summary, the secondary objectives of this study are to evaluate if surgical stabilization compared to non-surgical care result in outcome advantages such as health related quality of life, shorter time to return to work, less consumption of analgesics and fewer adverse events. Costs associated with the treatments will also be compared.

The secondary variables are listed below.

- Short Musculoskeletal Function Assessment (SMFA) is an instrument designed to measure the functional status of patients with various musculoskeletal disorders (Ponzer, Skoog et al. 2003). It consists of two parts, the dysfunction index based on 34 questions on difficulty performing certain

tasks, and the bother index based on 12 questions on how much the patients are bothered in certain areas of life. The dysfunction and bother indexes are calculated from the questions and range from 0 (best) to 100 (worst). SMFA is also distributed to patients with other types of fracture in the SFR.

- The EQ-5D-5L is a generic quality of life instrument and consists of five dimensions/questions concerning mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Burström, Teni et al. 2020). Each dimension has 5 answer alternatives: from no problems to extreme problems. An index can be calculated and depending on baseline value set used the index runs between approximately -0.2 (worst possible health) to 1.0 (best possible health). The EQ-5D-5L 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). EQ-5D-5L is distributed also to patients with other types of fracture in the SFR.

Surgical data and complications

- Detailed surgical data will be collected through the SFR, radiographs and hospital files. Additional spine surgeries (diagnosis and type of surgical procedure) will be identified in the SFR and the National Board of Health and Welfare National Patient Register (NPR). Inpatient admissions, hospital stay and adverse events (postoperative infection, deep vein thrombosis and pulmonary emboli) will be collected from the NPR.

Imaging: radiology and magnetic resonance imaging

Minimum study imaging and time points are as follows. For imaging details, see Appendix. Standard preoperative investigation involves a computer tomography (CT) and magnetic resonance imaging (MRI) of the injured and adjacent segments. All preoperative MRIs are interpreted at a central site. Non-surgically treated cases are as per standard routine investigated with a CT or standing radiograph at about two weeks. At the 3-4 month follow-up a CT is performed, as part of routine assessment. A CT and whole spine standing radiograph (coronal and sagittal) is performed at 12 months. MRI of the thoracolumbar spine is performed at 12 months. Degree of fracture compression, local and global kyphosis, adjacent segment degeneration, and extent of any soft tissue/ligamentous injuries will be registered.

Analgesics and antibiotics

- Collected doses of analgesics and antibiotics from pharmacies will be collected from the National Board of Health and Welfare Swedish Prescribed Drug Register in Sweden and from questionnaires and medical records in Norway.

Sick leave

- Data on sick leave will be collected from the Swedish Social Insurance Agency ('Försäkringskassan'). The 'Longitudinal integrated database for health insurance and labour market studies' available at Statistics Sweden may be used to retrieve data on unemployment and loss of income due to the fracture. In Norway the same data will be collected from questionnaires and medical records.

Mortality

- Mortality, including cause of death will be collected from the SFR and/or the National Board of Health and Welfare Mortality Register in Sweden. In Norway information on mortality will be collected from medical records.

7. STATISTICS

7.1. Sample size calculation

The primary outcome is the Oswestry Disablity Index (ODI) at 1 year. How large a difference in ODI should be between two groups to be clinically relevant is not known. Often the ODI minimal clinical difference (MCID) is used as an estimate of a clinically relevant group difference. MCID for ODI has been estimated to be around 10 (Copay, Glassman et al. 2008). In previous studies the SD for ODI is between 10 and 20, with lower values seen after surgical treatment of thoracolumbar fractures than after degenerative lumbar spine conditions (Copay, Glassman et al. 2008, Wei, Liu et al. 2010)..

To identify a minimal clinical important difference (MCID) in the ODI of 10 with a standard deviation of 20 with alpha=0.05 and power of 90%, a sample size of 84 patients in each group is needed. To account for a loss to follow-up of up to 20%, 101 patients in each group is needed in the randomized controlled trial.

7.2. Statistical analysis

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. Sensitivity analyses will be performed comparing the 'intention to treat' data against a per-protocol data, i.e. patients who exclusively complied with the treatment. Missing data will be handled with case-by-case exclusion/censoring.
To test differences in continuous variables measured on at least interval scale between two independent groups the Student’s t-test for uncorrelated means will be used. The non-parametrical Mann-Whitney test will be used to test non normal data. In order to evaluate hypotheses of variables in contingency tables, the Chi-square test will be used or, in the case of small, expected frequencies, Fisher's Exact Test. Regression analysis will be used in order to evaluate the dependency between variables and a correlation coefficient analysis will be used in order to test independence between variables. In addition to that 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. Independent statistical expertise will perform the statistical analysis.

Sick leave/time to return to work is measured by using data from the Swedish Social Insurance Agency (Försäkringskassan, https://www.forsakringskassan.se/statistik/kontakta-statistikenheten) in Sweden or data collected from questionnaires and medical records in Norway and will be stratified based on the presence or absence of sick leave before the fracture event. Data on total time on sick leave (full time or part time; variables “sjuk- och rehabiliteringspenning” or “sjuk- och aktivitetsersättning”) as well as the diagnosis used for sick leave will be collected. Analyses will be

performed for dichotomous data at different time points, 4 months and 1 year after the fracture with Chi-square tests and Fisher's exact tests.

Data on collected analgesics and antibiotics from pharmacies will be collected from the National Board of Health and Welfare Swedish Prescribed Drug Register (https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/lakemedelsregistret/) in Sweden and from questionnaires and medical records in Norway. Data from baseline until the 1-year follow-up will be collected as amount of collected analgesics. Since different opioids may be used, conversion to morphine equivalents may be done. Data on other analgesics will be collected. Data on any prescribed antibiotics will be collected. Data on costs for the prescribed pharmaceuticals will be collected. Anatomic Therapeutic Chemical classification system (ATC) codes will be used to group the pharmaceuticals. Collected prescriptions will be assessed as dichotomous data (collected/not collected) at different time intervals; 0 to 4 months, >4 months to 1 year with Chi-square tests. Total amount of collected opioids (continuous data consisting of morphine equivalents) will be compared with the Student's t-test or the Mann-Whitney test, depending on distribution.

Adverse events will be collected as (a) any spine surgery (and reason for) during the follow-up (from the SFR and the NPR in Sweden and by RedCap in Norway), (b) postoperative infection (from the SFR or diagnosed in the NPR based on diagnosis codes in Sweden and from questionnaires and medical records in Norway) and prescribed and collected antibiotics in close relation to the fracture (from the Swedish Prescribed Drug Register in Sweden and from questionnaires and medical records in Norway) during the follow-up. These will be analyzed as dichotomous variables with Chi-square or Fisher's exact tests.

Data on costs on the individual level will be collected. These consists of costs for the inpatient and outpatient visits (including surgery, radiographs, braces) collected from the treating hospital, analgesic and antibiotic treatments (collected from the Swedish Prescribed Drug Register in Sweden and from questionnaires and medical records in Norway), cost for sick leave (collected from the Swedish Social Insurance Agency and/or Statistics Sweden in Sweden and from questionnaires and medical records in Norway). Working status at baseline and at follow-ups will be collected from the 'Longitudinal integrated database for health insurance and labor market studies' available at Statistics Sweden for Swedish patients and the earnings lost due to the fracture will be estimated. In Norway patients will be asked to state the number of outpatient and telephone contacts (physician, nurse, physiotherapist) the fracture and treatment have resulted in at the 4 month and the 1-year follow-up. They will also be asked to state other expenses they have had in relation to the fracture and be asked to estimate the earnings lost due to the fracture. Quality-adjusted life years (QALYs) will be calculated for each group (as measured by EQ-5D-5L). Combining cost and QALY yields incremental cost-effectiveness ratio (ICER) of the surgical intervention as compared to non-surgical care. To quantify the uncertainty around estimates, bootstrapping will be used. This allows the creation of the cost-effectiveness plane (a chart showing differences in outcomes and costs on each axis).

This ICER will then be compared to commonly used estimates of ICERs of other interventions (mainly surgeries and pharmaceutical interventions). Given the uncertainty around the official thresholds of willingness to pay for healthcare interventions, a cost-effectiveness acceptability curve will be drawn, showing the likelihood of the surgical intervention of being cost-effective given different levels of willingness to pay.

In general, health economic evaluations should include the whole duration of effects a particular intervention has. If large differences between groups exist still at 1-year follow-up, a horizon effect could bias the results. A horizon effect makes interventions with high upfront costs and slow recuperation of these investments less attractive compared with cheap interventions with higher later costs and/or worse long-term health outcomes. A health-economic model populated with data from the SFR in Sweden, from RedCap, questionnaires and medical records in Norway and published sources will be created to estimate the possibility and extent of this bias. Also, the model will be used to correct for this bias.

7.2.1. Interim analyses

The study plan intends complete inclusion and 1-year follow-up before analysis, therefore an interim analysis is not planned.

8. DATA MANAGEMENT

8.1. Recording of data

Data will be collected from several sources (Table 2). Data primarily collected by the SFR will upon request from the research group be transferred from the SFR into the study database, with the exception of the screening question answers that will be entered into the study database from the SFR interface. Patient-reported outcome data will depending on type of data and time point be collected by the SFR or the central study coordinator.

Table 2. *Collection of data.*

Country	Sweden						Norway		
Collected by	Central study coordinator	SFR	Study database at SFR	NPR	Pharma-ceutical register	Social Insurance Agency /Statistics Sweden	Questionnaires and medical records	Hard disk drive	RedCap
Type of data									
ODI	X						X		
SMFA		X*					X		
EQ-5D-5L		X*					X		
Other questionnaire data	X						X		
Images	X							X	
Fracture classification		X							X
Screening question answers			X						X
Additional spine surgery		X		X					X
Adverse events				X			X		
Analgesics/antibiotics					X		X		
Sick leave data						X	X		

*Collected by central study coordinator at 3/4 months

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 from each participating study center, a copy of the completed study database, original protocol with amendments and the final report will be stored at the Karolinska University Hospital for a minimum period of 10 years after termination of the trial. All informed consents and data collected in Norway will be stored at each Norwegian study site for 5 years after the study ending.

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 coordinator will have regular contacts with the clinic to verify informed consents of participating subjects, to confirm that facilities remain acceptable, that the investigational team is adhering to the protocol, to verify inclusion/exclusion criteria, study main endpoints. The investigator 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 of the study group may perform audits or inspection at the center. The investigator must ensure that all study documents are accessible for auditing and inspection. The purpose of an audit or inspection is to examine all study-related activities and documents systematically and independently, 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 Ethical Review Authority has approved the study (dnr: 2021-00011, date of issue 2021-02-15, dnr: 2023-07942-02, date of issue 2024-01-02).

The Principal Investigator is responsible for informing the Ethics review board of any amendment to the protocol, in accordance with local requirements.

10.1. Informed consent

The investigator at each center 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 original, signed Informed Consent Form (ICF) must be stored at the study site. For Swedish patients, a copy of the signed ICF is kept by the central study location. In Norway, a copy of the signed ICF will be stored at the respective trial centers.

The monitor(s) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject is authorizing such access.

10.2. 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.

10.3. Insurances

The study subjects are covered by the Swedish Patient Injury Act in Sweden and by Norwegian System of Patient Injury Compensation in Norway.

11. PROTOCOL DEVIATIONS AND AMENDMENTS

Modifications to the signed protocol are only possible through approved protocol amendments and with the agreement of all responsible persons. 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 concerned Ethics Committee must be informed and should be asked for its opinion/approval prior 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 relevant ethics committee, 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).

databases/registries and will be stored in a computer database, maintaining confidentiality in accordance with national data legislation.

11.1. Amendments

The protocol has been updated 2023-01-19 with added study sites in Sweden, including Halmstad, Jönköping, Kalmar and Västerås, and Norway, including Akershus, Bergen, Oslo, and Stavanger. Sentences describing how the study design and data collection are modified for Norwegian patients have been added to Synopsis, 1.1, 3.1, 3.2, 3.3, 4.3, 4.5, 5.4, 6.1, 6.2, 7.2, 8.1, 10.1 and 10.3.

The protocol has been updated 2023-07-16 with added study site in St Olavs Hospital in Norway.

The wording of section 5.1. about surgical treatment has been adjusted to clarify that posterior fixation is the recommended treatment, but other surgical methods are allowed within the study to the surgeon's discretion.

Information clarifying when treatment cross-over is acceptable within the study has been added to 5.4.2 with the heading "Treatment cross-over control group".

The dnr from The Swedish Ethical Review Authority has been corrected from 2020-00011 to 2021-00011 in section 10.

The protocol has been updated 2024-05-21. The update includes change of Research Body from Karolinska Hospital to Uppsala University, added ethical amendment in section 10. and updated contact details.

Information about the authorship guidelines that will be followed for the final manuscript have been added to section 12.1.

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 either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.1. Authorship

The ICMJE guidelines for authorship (ICMJE) will be implemented in the writing and publication of the final report and any side-projects that uses the trials database. Minimum requirements include:

- Substantial contributions to the design of the trial and/or contribution with data from at least 5 patients in the trial
- Drafting the work or revising it critically for important intellectual content
- Final approval of the final manuscript and choice of journal
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

All participating investigators that don't fulfil all four criteria will be mentioned as part of the SunBurst study group.

13. STUDY TIMETABLE

13.1. Study period

Estimated subject enrollment start: 2021-09-01

Estimated subject enrollment stop: 2025-12-31
Estimated subject last 1-year follow-up: 2026-12-31
Estimated study end: 2036-12-31

13.2. Definition of “End of study”

End of study is defined as the last follow-up of the last subject.

14. LIST OF REFERENCES

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Appendix 1 - Imaging

Imaging: radiology and magnetic resonance imaging

Computed tomography (CT)
CT is performed of the fractured area according to clinical routines at the participating hospitals and should include at least one follow-up at 3 to 4 months. An additional CT is performed at the 1-year follow-up. The CT must include the fractured vertebra/es and two vertebras above and below.

Magnetic Resonance Imaging (MRI)
MRI is performed according to clinical routine at the time of the fracture. An additional MRI is performed at the 1-year follow-up. A specific protocol has been developed for optimal imaging of soft tissues and is available from the department of radiology, Uppsala University Hospital (please contact Hernani Vieira by mail: hernani.vieira@surgsci.uu.se, or by telephone: 018-6119879 to acquire the protocol). We encourage its use for all patients with vertebral fractures.

Standing radiographs
A standing anteroposterior (or posteroanterior) and sagittal whole spine radiograph is taken at the 1-year follow-up. The examination must be calibrated (to allow distance measuring).

Measurements on images
Degree of fracture compression, local and global kyphosis, adjacent segment degeneration, and extent of any soft tissue injuries will be registered.

The degree of fracture compression is measured as the percentage of anterior vertebral compression compared to the adjacent intact vertebrae seen on the sagittal view. The formula described by Keynan et al. will be used (Keynan, Fisher et al. 2006).

$[(V1 + V3)/2 - V2]/(V1 + V3)/2)$
V1 = intact vertebra above fracture
V2 = fractured vertebra
V3 = intact vertebra below fracture

Local kyphosis is measured according to the sagittal Cobb angle, i.e, the angle of a line parallel to the superior endplate of the vertebra above the fracture and a line parallel to the inferior endplate of the vertebra below the fracture (Polly, Kilkelly et al. 1996, Keynan, Fisher et al. 2006)

Global kyphosis is measured as the angle of a line parallel to the superior endplate of the maximally tilted superior vertebra and a line parallel to the inferior endplate of the maximally tilted inferior endplate seen on the sagittal whole standing radiograph.

Adjacent segment degeneration is registered as any form of listhesis, disc herniation or degeneration, hypertrophic facet joints and spinal stenosis seen on MRI 1 year after fracture compared to the initial MRI performed before randomization (Park, Garton et al. 2004, Kuo, Huang et al. 2018). Vertebrae above and below the fracture, or above and below the fixation in case of surgically treated patients, will be analyzed.

Soft tissue injuries of the posterior tension band will be registered on the initial MRI scan. The posterior tension band consists of the following structures:

- Supraspinous ligament
- Interspinous ligament
- Ligamentum flavum
- Facet capsules
- Thoracolumbar fascia

Each structure will be categorized as intact, incompletely disrupted or disrupted (Vaccaro, Rihn et al. 2009). 'Intact' indicates no change in MRI signal. 'Incompletely disrupted' indicates that there is a visible change in MRI signal such as edema, but complete disruption cannot be identified with certainty. 'Disrupted' indicates that there is a clear change in MRI signal compatible with a definite disruption. The posterior tension band as a whole will be categorized as intact or indeterminate. Patients with complete disruption of the posterior tension band are not eligible for the study.

Appendix 2 – ICD and KVÅ codes

Possible diagnostic codes

ICD-10 code	Description in Swedish
	Medicinska komplikationer
I26	I26.0: Lungemboli med uppgift om akut cor pulmonale. I26.9: Lungemboli utan uppgift om akut cor pulmonale
I80	Flebit och tromboflebit i ven
I20-I25	Ischemiska hjärtsjukdomar (inklusive detaljerade diagnoser)
N39.0	Urinvägsinfektion utan angiven lokalisation
N30.9	Cystit ospecificerad
N30.0	Akut cystit
J13-J17.0 + J18	Pneumoni (ospec + olika bakteriella agens)
	Kovariater
I20-I25	Ischemiska hjärtsjukdomar (inklusive detaljerade diagnoser)
E10-E14	Diabetes
	Kirurgiska komplikationer
M84.1J	Utebliven läkning/pseudartros i torakalryggen
M84.1K	Utebliven läkning/pseudartros i ländryggen
T81.0	Blödning/hematom
T81.4	Infektion efter kirurgiska och medicinska ingrepp som ej klassificeras på annan plats (sårinfektion)
T81.8	Annan specificerad komplikation till kirurgiska och medicinska ingrepp som ej klassificeras på annan plats
T81.8W	Annan specificerad komplikation till kirurgiska och medicinska ingrepp som ej klassificeras på annan plats
T84.2	Mekanisk komplikation av instrument för inre fixation av andra skelettben

Possible surgical codes

ICD-10 code/Klassifikation av vårdåtgärder (KVÅ)	Description in Swedish
ABC33	Dekompression av nervrötter i bröstryggraden
ABC36	Dekompression av nervrötter i ländryggraden
ABC53	Dekompression av ryggmärgen och nervrötter i bröstryggraden
ABC56	Dekompression av ryggmärgen och nervrötter vid degenerativa förändringar i ländryggraden
ABC63	Dekompression av ryggmärgen i bröstryggraden
ABC66	Dekompression av ryggmärgen i ländryggraden
ABC99	Annan dekompressiv operation av ryggmärgen eller nervrötter
AWW99	Annan reoperation på nervsystemet
NAG39	Främre fusion utan fixationsmaterial
NAG49	Främre fusion med intern fixation
NAG69	Bakre fusion utan fixation
NAG79	Bakre fusion med fixation
NAG99	Annan excision, rekonstruktion eller fusion av leder i kotpelare
NAJ89	Osteosyntes av fraktur i kotpelare med annan eller kombinerad metod
NAS99	Annan operation vid infektion i kotpelare
NAT29	Bakre korrektion av deformitet
NAT19	Främre korrektion av deformitet
NAK19	Partiell eller total excision av kota
NAU49	Extraktion av implantat/osteosyntesmaterial
NAW49	Sutur av sårruptur i kotpelare eller nacke
NAW59	Reoperation för ytlig infektion i kotpelare eller nacke
NAW69	Reoperation för djup infektion i kotpelare eller nacke
NAW89	Reoperation för djup blödning i kotpelare eller nacke
NAW99	Annan reoperation i kotpelare eller nacke