Statistical Analysis Plan

Cost-Effectiveness of Decompression with vs without Fusion in Lumbar Degenerative Spondylolisthesis

The NORDSTEN-DS trial, NCT02051374

SAP Version 2.0

Date 03.02.2025

Approval Page

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Abbreviations

CNT	Cost needed to treat
CT	Computed tomography
CEAF	Cost-effectiveness acceptability frontier
DA	Decompression alone
DF	Decompression with an additional fusion
EQ-5D	EuroQol 5-dimensional questionnaire utility index
EVPI	Expected Value of Perfect Information
FU	Follow-up
ICER	Incremental Cost-effectiveness
LMM	Linear mixed model
LSS	Lumbar spinal stenosis
MICE	Multivariate Imputation by Chained Equations
MRI	Magnetic resonance imaging
NNT	Number needed to treat
NRS	Numerical rating scale
ODI	Oswestry disability index
PROMs	Patient reported outcome measures
QALY	Quality-Adjusted Life Years
SAP	Statistical Analysis Plan

AMENDMENTS

The main purpose of the present SAP is a supplement to the original study protocol (Version 1.0), received by CinicalTrials.gov on January 10, 2014 (Identifier, NCT02051374). There is one amendment regarding the eligibility criteria. The trial originally (April 15, 2014) excluded patients with ODI scores under 25. Based on the experience of participating surgeons, a considerable number of patients were not eligible for inclusion, even though their leg and back complaints justified an operation. To enhance the study's external validity, the steering committee decided that, from August 29, 2015, patients should no longer be excluded for ODI scores under 25.

The health economic analysis makes one significant addition to the published trial protocol; in addition to estimating costs from the healthcare perspective, we have included costs from the societal perspective.[1 2]

INTRODUCTION

Background and rationale

Degenerative spondylolisthesis (DS) is defined as a forward slippage of one vertebra over another without a disruption in the vertebral arch.[3] Most patients present symptoms related to concomitant spinal stenosis, typically back and leg pain in the supine position.[4 5]

Former studies, meta-analyses, and systematic reviews suggested moderate evidence or a tendency towards better outcomes when decompression was combined with fusion.[5-8] More recent registry studies, controlled randomized trials (RCTs), and systematic reviews have found contradictory evidence; concluding that additional fusion does not give superior clinical results when operating for DS.[9-15]

A comprehensive economic evaluation of the relative cost-effectiveness of decompression alone (DA) and decompression with instrumented fusion (DF) has not been conducted in a randomised controlled trial. The present document describes the plan for the cost-effectiveness analysis embedded in the Norwegian Degenerative Spondylolisthesis and Spinal Stenosis (NORDSTEN-DS) trial.[10] The objective of this study is to compare the cost-effectiveness of DA and DF for the management of DS. Analysis will be conducted from a healthcare and societal perspective.[2] We will utilize data from the trial collected from baseline to 5 years after surgery.

METHODS

We introduced the method for this cost-effectiveness study at ClinicalTrials.gov and in the published study protocol.[16] A summary of the methods and an extended description of the planned statistical analyses are presented below. More information regarding the general trial methods of NORDSTEN-DS has been provided elsewhere.[10 16]

Study design and overview

This cost-effectiveness analysis will be embedded in the NORDSTEN-DS trial, a 1:1 block randomized, investigator-initiated, open-label, multicentre, non-inferiority trial. Patients were included in the trial from April 2014 until November 2017. Data has been collected at baseline, three months, one year, two years, and five years postoperatively.

The trial has been monitored following a modified version of The International Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP).[17] The trial was first registered on ClinicalTrials.gov on January 10, 2014 (Identifier: NCT02051374). The SPIRIT checklist[18] was used as a template for the published trial protocol (version 3.0).[16] The protocol has been approved by the Norwegian Committee for Medical and Health Research Ethics Midt (2013/366). The statistical analysis plan for the cost-effectiveness analysis has been prepared in accordance with guidelines for statistical analysis plans in clinical trials.[19] The reporting of this cost-effectiveness analysis will be based on an adapted Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[20] and the Panel on Cost-Effectiveness in Health and Medicine guidelines.[2 21]

Participants

Sixteen Norwegian orthopaedic and neurosurgical hospital departments have included patients in the NORDSTEN-DS trial. Criteria for inclusion and exclusion are given in Table 1.

Patients received oral and written information about the study and the alternative treatment options. All patients willing to participate signed an informed consent form. If a patient did not

want to participate, they were treated following the hospital's established procedures. More information is provided elsewhere.[10 16]

The flow of participants through the study will be reported with a Consolidated Standards of Reporting Trials Statement (CONSORT) trial flow chart.

Table1

Inclusion criteria: To be eligible for the study the participants should:	**Exclusion criteria:** Patients were excluded from the study if they:
Be over 18 years of age.	Are not willing to give written consent.
Understand Norwegian language, spoken and written.	Are participating in another clinical trial that may interfere with this trial.
Have a spondylolisthesis, with a slip >=3 mm, verified on standing plain x-rays in lateral view.	Are ASA- grade > 3.
Have a spinal stenosis in the level of spondylolisthesis, shown on MRI, CT scan or myelogram.	Are older than 80 years.
Have clinical symptoms of spinal stenosis as neurogenic claudication or radiating pain into the lower limbs, not responding to at least 3 months of qualified conservative treatment.	Are not able to fully comply with the protocol, including treatment, follow-up or study procedures (psychosocially, mentally and physically).
Be able to give informed consent and to respond to the questionnaires.	Have cauda equina syndrome (bowel or bladder dysfunction) or fixed complete motor deficit.
	Have a slip >=3 mm in more than one level.
	Have an isthmic defect in pars interarticularis.
	Have a fracture or former fusion of the thoracolumbal region.
	Have had previous surgery in the level of spondylolisthesis.
	Have a lumbosacral scoliosis of more than 20 degrees verified on AP-view.
	Have distinct symptoms in one or both legs due to other diseases, e.g. polynevropathy, vascular claudication or osteoarthtritis.
	Have radicular pain due to a MRI-verified foraminal stenosis in the slipped level, with deformation of the nerve root because of a bony narrowing in the vertical direction.

MRI = Magnetic resonance imaging, CT = Computed tomography, AP = anterior- posterior, ASA = American Society of Anesthesiologists score: score of 1 indicates the presence of no disease, 2 the presence of mild systemic disease, 3 the presence of severe but not life-threatening systemic disease, 4 the presence of severe systemic disease that is a constant threat to life, and 5 a moribund patient who is not expected to survive beyond the next 24 hours without surgery

Allocation

The computer-generated 1:1 randomisation was block-permuted and centre-stratified. After the patient had signed the informed consent form, the randomisation was performed within 6 weeks before treatment. The computer-generated randomisation procedure was concealed and administered by a central coordinator.

Interventions

Decompression alone (DA): Posterior approach with mid-line preserving decompression.

Decompression followed by fusion with instrumentation (DF): Posterior approach with decompression, followed by bone grafting and posterolateral pedicle screw fixation with or without an additional intervertebral cage.

Details are provided elsewhere.[10]

Data collection

Table 2 shows an overview of data collection. At baseline, three months, one year, two years, and five years the participants responded to self-reported questionnaires (the LK forms) which include demographic variables, variables regarding work status, utilization of pain medication, and a set of patient-reported measures, including the EQ-5D-3L[22] and the ODI.[23] Data on surgical method, postoperative complications, and length of hospital stay were collected from the surgeon forms, the patient forms (LK forms, which were filled out by the patients), and the Case Report Forms (CRFs, which were filled out by study coordinators) compiled at hospital stay, from the CRF and LK forms at three months and two and five years, and from the LK forms at one year. All information is stored at the Clinical Trial Unit at Oslo University Hospital (OUH), Norway, and will be analysed through the Service for Sensitive Data (TSD) at OUH. Table 2 shows the source and time point of the data collection. More information regarding data collection is provided elsewhere.[10]

	Forms		Time points				
Table 2. Method and time point of data collection	CRF or Surgeon forms	LK forms	Baseline incl. hospital stay	3 months	1 year	2 years	5 years
Patient characteristics							
Age		x	x				
Gender		x	x				
Education		x	x				
Marital status		x	x				
Smoking habits		x	x				
Body mass index		x	x				
Comorbidities (ASA grade)	x		x				
Duration of symptoms		x	x				
Use of analgesics		x	x				
Employment status		x	x	x	x	x	x
Effect measures							
EQ-5D-3L		x	x	x	x	x	x
ODI		x	x	x	x	x	x
Cost measures							
Index radiology	x		x				
Index surgery	x		x				
Surgical method	x		x				
Duration of surgery	x		x				
Duration hospital stay	x		x				
Postop complication ex. reop	x		x	x	x	x	x
Primary healthcare utilization							
General practitioners	x			x	x	x	
Physiotherapists	x			x	x	x	
Chiropractors	x			x	x	x	
Acupuncture	x			x	x	x	
Other	x			x	x	x	
Radiology (X-ray and/or MRI)	x			x		x	x
Subsequent surgery/reoperation	x			x	x	x	x
Re-admission to hospital	x			x	x	x	x
Admission to out-patient clinic	x			x	x	x	x
Pain medication		x	x	x	x	x	x
Employment status		x	x	x	x	x	x

Variables and measurements

Descriptive

Included participants will be described with respect to age, gender, education, marital status, smoking habits, body mass index, former spine operation, comorbidities including the American Society of Anesthesiologists (ASA) score, duration of symptoms, use of analgesics, PROM scores, surgical techniques, duration of surgery, length of hospital stay, complications, and subsequent surgeries at index level or at an adjacent lumbar level.

Effectiveness measures

Quality Adjusted Life Years (QALYs) will be the primary effectiveness measure. Health state of the participants will be assessed by the 3-level version of the EuroQol-5 Dimensions (EQ-5D-3L).[24] The UK tariff will then be used to convert health states into utility scores (range, -0.59 to 1), anchored at 0 "death" and 1 "perfect health", with negative values representing health states perceived to be worse than death.[24] The QALY is the product of the measurement of health-related quality of life (here EQ-5D-3L) and duration of life. For example, if a patient reports a mean change in EQ-5D of 0.3 in a period of 5 years, they will have gained 1.5 QALY units. Costs and health effects will be discounted at an annual rate of 4%, as recommended by Norwegian pharmacoeconomic guidelines.

(https://www.dmp.no/globalassets/documents/offentlig-finansiering-og-pris/dokumentasjon-til-metodevurdering/submission-guidelines-april2024.pdf.)

Cost measures

Healthcare utilisation due to the index surgery during hospital stay will be retrieved from the surgeon forms and the CRF forms and includes preoperative and postoperative radiology, index surgical method, subsequent surgical method, surgical and postoperative complications, and length of hospital stay. Healthcare utilization within the follow-up period will be retrieved from

the LK and CRF forms which include consultations within primary care (GP, physiotherapy, chiropractor, acupuncture, and others), secondary/tertiary care (radiology, subsequent surgery/reoperations, re-admission to hospital, and admission to out-patient clinics), and use of pain medication. Productivity loss within the follow-up period will be retrieved from the LK forms and will include absenteeism due to sick leave, work assessment allowance, and disability benefits.

Cost of healthcare utilization per person will be estimated by multiplying frequency of use by unit costs collected from national tariffs. Cost of productivity loss per person will be estimated by multiplying number of workdays with complete productivity loss by an estimated average wage rate including taxes and social costs (from official statistics in Norway) (Table 3).

We will estimate all unit costs based on 2024 prices, recalculated to euros using the exchange rate from the Norwegian Bank of Norway from May 15, 2024.

We will make the following assumptions when estimating the various cost measures:

Health care utilization:

The costs of the index surgery, subsequent surgeries, and follow-up visits for standard clinical practice (not including extra visits to trial coordinators and for extra trial radiology) will be estimated using standard unit costs collected from national pricelists, i.e., the total reimbursement according to the Norwegian diagnosis related group (DRG) system. We will calculate the reimbursement according to an ISF (Norwegian abbreviation for activity-based funding) rate for each patient. The ISF rates for health care procedures (surgery, radiology, examination at outpatient clinics, etc.) are based on a set of International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) primary and secondary diagnosis codes combined with a set of ICD-10 procedure codes (main procedure and additional procedures).

Productivity loss:

The human capital approach will be used to estimate productivity costs. The human capital approach estimates productivity costs by multiplying the number of workdays lost, adjusted for the degree of absence, by the average age- and gender-adjusted gross daily wage.[25 26]

The trial collects data on employment status, with responses categorized as: at work, on sick leave, work assessment allowance, staying at home unpaid, student, unemployed, on disability benefits, or retired. We will make the following assumptions when estimating work absence:

1. If work status is the same at consecutive time points, it is assumed to be unchanged between those points.
2. If the status changes between points, the midpoint is used to estimate the transition and productivity loss.
3. Patients reported as retired are assumed to have zero productivity loss thereafter.

Trial data includes information on employment status with the following responses alternatives registered on the Patient Form: 1) At work; 2) Sick leave (percentage degree of absence); 3) Work assessment allowance; 4) Staying at home, unpaid; 5) Student/school pupil; 6) Unemployed; 7) Disability benefits (percentage degree of absence); 8) Retired pensioner.

The data does not include information on the periods between different time points, so we have to make some assumptions: If a patient reports the same work status at two consecutive measurement points, they are assumed to have had the same work status during the entire period between the two measurement points. If the patient reports a different work status at two consecutive measurement points, the alternative "On sick leave" and "If reported healthy, enter date" will be used to estimate the type and length of productivity loss. If the patient reports that they are a pensioner at a measurement point, they will subsequently be registered with zero weeks of lost productivity. If the reported employment status is similar at two consecutive time points, we will assume that employment status has been constant between

the time points. If patients report different status from one time point to the next, we will estimate a mean productivity loss based on data from the two time points, i.e., transition between different statuses occurs at the mid-point between the two time points.

Pain medication:

Trial data captures the usage of pain medication, including frequency categories at baseline and several follow-up points, but lacks detail on the period between assessments. To estimate costs, we will assume:

1. If frequency is missing at a time point, it is inferred from other available data for the patient.
2. If frequency is the same at consecutive points, it is assumed to remain consistent during the interval.
3. If frequency changes, we assume a midpoint consumption rate between the two frequencies.

For cost estimation:

- **Less than monthly:** Treat as 2 days of use in 3 months.
- **Monthly:** 6 days in 3 months.
- **Weekly:** 26 days in 3 months.
- **Daily and several times a day:** 91 days in 3 months.

We categorize medications into price classes for cost estimations:

- **Price Class B (infrequent use):** Average cost of two doses combining Paracetamol, Ibuprofen, and Tramadol hydrochloride.

- **Price Class A (frequent use):** Average cost of five typical three-times-a-day combinations, including Paracetamol, Ibuprofen, Tramadol hydrochloride, and Gabapentin.

These assumptions simplify our calculations and reflect typical medication patterns, while acknowledging the relatively low cost impact of pain medications.

Postoperative primary care:

Trial data includes the patients' responses to the questions "Have you had other treatment (General practitioners, Physiotherapists, Chiropractors, Acupuncture, Other) for your spine condition?" and "If yes, how many times?" Costs will be estimated using Norwegian national tariffs. Costs for visits to practitioners will be taken from https://normaltariffen.no for general practitioners (tariff 2ad) and for contract specialists (tariff 3ad). These tariffs, which are based on fees and deductibles, should be multiplied by 2 to account for additional public funding. For visits to physiotherapists we will use a similar approach using tariffs taken from https://lovdata.no/dokument/SF/forskrift/2024-06-17-1184/KAPITTEL_2#KAPITTEL_2, i.e., tariff A1a, multiplied by 2 to account for additional public funding. For treatment with manipulation (i.e., chiropractor) and acupuncture we will use mean taxes from different Norwegian private practitioner price lists (https://prisnorge.no).

Table 3. Resource use and costs

Cost categories	Unit	Unit price (NOK)	Unit price (euro)	Reference (source)
Preoperative outpatient clinic	Per visit			DRG
Primary surgery				
Decompression alone without comorbidity or complications	Per surgery			DRG
Decompression with comorbidity or complications	Per surgery			DRG
Decompression with fusion without comorbidity or complications	Per surgery			DRG
Decompression with fusion with comorbidity or complications	Per surgery			DRG
Subsequent surgery	Per surgery			DRG
Reoperation without fusion without comorbidity[a] or complications[b]	Per surgery			DRG
Reoperation without fusion with comorbidity or complications	Per surgery			DRG
Reoperation with fusion without comorbidity or complications	Per surgery			DRG
Reoperation with fusion with comorbidity or complications	Per surgery			DRG
Radiology				
MRI	Per exam			Private institutes, estimated average
X-ray	Per exam			Private institutes, estimated average
CT scan	Per exam			Private institutes, estimated average
Outside hospital stay during follow-up				
Primary care				
General practitioners	Per visit			https://normaltariffen.no/
Physiotherapists	Per visit			https://lovdata.no/dokument/SF/forskrift/2024-06-11184/KAPITTEL_2#KAPITTEL_2
Chiropractors	Per visit			Private practitioner price lists, estimated average
Acupuncture	Per visit			Private practitioner price lists, estimated average
Secondary/tertiary care				
Re-admission hospital	Per day			DRG
Admission out-patient clinic	Per visit			DRG
Rehabilitation	Per day			DRG
Radiology				
MRI	Per exam			Private institutes, estimated average
X-ray	Per exam			Private institutes, estimated average
CT scan	Per exam			Private institutes, estimated average
Productivity loss				
Work absenteeism	Per work day			Average wage from Statistics Norway
Disability benefits	Per work day			Average wage from Statistics Norway
Pain medication	Per daily defined dose			Norwegian Medical Products Agency

[a]Comorbidity: urogenital, cardiopulmonary (e.g., chronic obstructive lung disease, atrial fibrillation)
[b]Complications: cardiopulmonary, anaphylactic reaction, blood transfusion, liquor leakage, superficial infection, thromboembolic episode, urological
[c]

Sample size

The sample size was computed according to the primary outcome of the clinical efficacy trial in which the proposed number of required participants (256 patients) was based on a non-inferiority trial design with a binary primary outcome (an ODI improvement of 30 or more), a non-inferiority margin of 15%, α= 0.95, β=0.80, and a proposed dropout rate of 10%.[10] For this cost-effectiveness analysis, the sample size is determined by the completeness of data pertaining to the research question.

Analytical approach

All analyses described in this SAP are considered a priori as they have been defined in the protocol and/or in this SAP prior to any analysis being conducted. All post hoc analyses will be identified as such in the article if relevant. All analyses will be carried out using SPSS, Stata, R, or other appropriate software. All analyses will be conducted in a modified intention-to-treat set (i.e., patients who were operated in accordance with the randomization and have available data after randomization). The health economist responsible for the statistical analyses will not have access to the data until the SAP is published (ClinicalTrials.gov, Identifier, NCT02051374), and will be unaware of the treatment-group assignment when conducting the analyses.

The primary cost-effectiveness (CE) measurement will be estimated by dividing the mean group difference in costs by the mean difference in QALYs gained (CostsDF minus CostsDA) divided by (QalyDF minus QalyDA). The results will be presented as an incremental cost-effectiveness ratio (ICER), meaning the difference in cost between decompression with fusion and decompression without fusion for each unit of effectiveness (QALY) gained.

To address missing data on costs and EQ-5D-3L scores, Multivariate Imputation by Chained Equations (MICE) will be implemented.[27] MICE is a statistical technique that replaces missing data with simulated values, thereby avoiding potential bias and facilitating intention-

to-treat analyses. The simulated values are drawn from a series of iterative regression models for each variable with missing data, each conditioned on all the other variables in the imputation model. Predictive mean matching, a Bayesian procedure that involves sampling the observed values closest to the predicted means from the regression models, will be used to impute missing costs and EQ-5D-3L scores by treatment arm. If not restricted by multicollinearity, we will in the imputation procedure include treatment site, age, gender, ASA grade, education, smoking status, body mass index, occupational status, use of analgesics, Hopkins Symptom Checklist-25, all variables collected at baseline, and values on EQ-5D, ODI, NRS leg pain, NRS back pain, and costs at each time point. To address the complete absence of primary care resource utilization data at the 5-year mark, we will utilize data from the 2-year follow-up to estimate 5-year utilization, under the assumption that resource use stabilizes over time. A sensitivity analysis will also be conducted by excluding these costs to assess the robustness of the results.

Multiple imputation will be combined with nonparametric bootstrapping to account for skewness, non-normality, and the correlation between costs and QALYs.[28] Linear regression models will be fitted to each bootstrapped dataset to obtain adjusted estimates of mean total costs and QALYs for each treatment arm. These regression models will adjust the mean total costs and QALYs for baseline values, treatment site, and patient characteristics, such as age and gender.[28 29]

Total and incremental adjusted costs and QALYs will be summarized by presenting means, standard errors, and 95% confidence intervals. Uncertainty about the ICER will be adressed by constructing a cost-effectiveness acceptability frontier (CEAF), which indicates the probability of the optimal intervention being cost-effective given a range of different willingness-to-pay thresholds.[30] Expected Value of Perfect Information (EVPI) will be

computed to provide an upper boundary on the potential value of conducting further research to reduce uncertainty.[31]

REFERENCE LIST

1. Neumann PJ, Sanders GD. Cost-Effectiveness Analysis 2.0. *New England Journal of Medicine* 2017;376(3):203-05. doi: 10.1056/NEJMp1612619
2. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 2016;316(10):1093-103. doi: 10.1001/jama.2016.12195
3. Farfan HF. - The pathological anatomy of degenerative spondylolisthesis. A cadaver study. - *Spine (Phila Pa 1976)1980 Sep-Oct;5(5):412-8* 2012:Oct.
4. Fitzgerald JA, Newman PH. Degenerative spondylolisthesis. *J Bone Joint Surg Br* 1976;58(2):184-92. [published Online First: 1976/05/01]
5. Watters WC, 3rd, Bono CM, Gilbert TJ, et al. An evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spondylolisthesis. *Spine J* 2009;9(7):609-14. doi: 10.1016/j.spinee.2009.03.016
6. Martin CR, Gruszczynski AT, Braunsfurth HA, et al. The surgical management of degenerative lumbar spondylolisthesis: a systematic review. *Spine (Phila Pa 1976)* 2007;32(16):1791-8. doi: 10.1097/BRS.0b013e3180bc219e [published Online First: 2007/07/17]
7. Resnick DK, Watters WC, 3rd, Sharan A, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 9: lumbar fusion for stenosis with spondylolisthesis. *J Neurosurg Spine* 2014;21(1):54-61. doi: 10.3171/2014.4.spine14274 [published Online First: 2014/07/02]
8. Steiger F, Becker HJ, Standaert CJ, et al. Surgery in lumbar degenerative spondylolisthesis: indications, outcomes and complications. A systematic review. *Eur Spine J* 2014;23(5):945-73. doi: 10.1007/s00586-013-3144-3 [published Online First: 2014/01/10]
9. Austevoll IM, Gjestad R, Solberg T, et al. Comparative Effectiveness of Microdecompression Alone vs Decompression Plus Instrumented Fusion in Lumbar Degenerative Spondylolisthesis. *JAMA Netw Open* 2020;3(9):e2015015. doi: 10.1001/jamanetworkopen.2020.15015 [published Online First: 2020/09/11]
10. Austevoll IM, Hermansen E, Fagerland MW, et al. Decompression with or without Fusion in Degenerative Lumbar Spondylolisthesis. *New England Journal of Medicine* 2021;385(6):526-38. doi: 10.1056/NEJMoa2100990
11. Forsth P, Michaelsson K, Sanden B. Fusion Surgery for Lumbar Spinal Stenosis. *N Engl J Med* 2016;375(6):599-600. doi: 10.1056/NEJMc1606502 [published Online First: 2016/08/11]
12. Inose H, Kato T, Sasaki M, et al. Comparison of decompression, decompression plus fusion, and decompression plus stabilization: a long-term follow-up of a prospective, randomized study. *Spine J* 2022;22(5):747-55. doi: 10.1016/j.spinee.2021.12.014 [published Online First: 20211225]

13. Kaiser R, Kantorová L, Langaufová A, et al. Decompression alone versus decompression with instrumented fusion in the treatment of lumbar degenerative spondylolisthesis: a systematic review and meta-analysis of randomised trials. *J Neurol Neurosurg Psychiatry* 2023 doi: 10.1136/jnnp-2022-330158 [published Online First: 20230227]
14. Shen Z, Guan X, Wang R, et al. Effectiveness and safety of decompression alone versus decompression plus fusion for lumbar spinal stenosis with degenerative spondylolisthesis: a systematic review and meta-analysis. *Ann Transl Med* 2022;10(12):664. doi: 10.21037/atm-22-2208
15. Wei F-L, Zhou C-P, Gao Q-Y, et al. Decompression alone or decompression and fusion in degenerative lumbar spondylolisthesis. *eClinicalMedicine* 2022;51 doi: 10.1016/j.eclinm.2022.101559
16. Austevoll IM, Hermansen E, Fagerland M, et al. Decompression alone versus decompression with instrumental fusion the NORDSTEN degenerative spondylolisthesis trial (NORDSTEN-DS); study protocol for a randomized controlled trial. *BMC Musculoskelet Disord* 2019;20(1):7. doi: 10.1186/s12891-018-2384-0 [published Online First: 2019/01/07]
17. ICH, Harmonised, Tripartite, Guideline. Guideline for good clinical practice E6(R1). June 1996. *http://wwwichorg/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guidelinepdf* 2014
18. Agha RA, Altman DG, Rosin D. The SPIRIT 2013 statement--defining standard protocol items for trials. *Int J Surg* 2015;13:288-91. doi: 10.1016/j.ijsu.2014.12.007 [published Online First: 2014/12/17]
19. Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA* 2017;318(23):2337-43. doi: 10.1001/jama.2017.18556 [published Online First: 2017/12/21]
20. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ : British Medical Journal* 2013;346:f1049. doi: 10.1136/bmj.f1049
21. Sanders GD, Maciejewski ML, Basu A. Overview of Cost-effectiveness Analysis. *JAMA* 2019;321(14):1400-01. doi: 10.1001/jama.2019.1265
22. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16(3):199-208. [published Online First: 1990/11/05]
23. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa 1976)* 2000;25(22):2940-52; discussion 52. [published Online First: 2000/11/14]
24. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35(11):1095-108. doi: 10.1097/00005650-199711000-00002
25. Zhang W, Bansback N, Anis AH. Measuring and valuing productivity loss due to poor health: A critical review. *Soc Sci Med* 2011;72(2):185-92. doi: 10.1016/j.socscimed.2010.10.026 [published Online First: 20101118]
26. Krol M, Brouwer W. How to estimate productivity costs in economic evaluations. *Pharmacoeconomics* 2014;32(4):335-44. doi: 10.1007/s40273-014-0132-3
27. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Softwar* 2011;45:1-67.
28. Ben Â J, van Dongen JM, El Alili M, et al. Conducting Trial-Based Economic Evaluations Using R: A Tutorial. *Pharmacoeconomics* 2023;41(11):1403-13. doi: 10.1007/s40273-023-01301-7 [published Online First: 20230717]
29. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;14(5):487-96. doi: 10.1002/hec.944

30. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;10(8):779-87. doi: 10.1002/hec.635
31. Heath A, Kunst N, Jackson C. Value of Information for Healthcare Decision-Making. *1st edition Boca Raton: Chapman and Hall/CRC, 2024* 2024(Epub ahead of print 8 February 2024.) doi: 10.1201/9781003156109.