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ORIGINAL ARTICLE

The Norwegian degenerative spondylolisthesis and spinal stenosis (NORDSTEN) study: study overview, organization structure and study population

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Abstract

Purpose To provide an overview of the The Norwegian Degenerative spondylolisthesis and spinal stenosis (NORDSTEN)-study and the organizational structure, and to evaluate the study population.

Methods The NORDSTEN is a multicentre study with 10 year follow-up, conducted at 18 public hospitals. NORDSTEN includes three studies: (1) The randomized spinal stenosis trial comparing the impact of three different decompression techniques; (2) the randomized degenerative spondylolisthesis trial investigating whether decompression surgery alone is as good as decompression with instrumented fusion; (3) the observational cohort tracking the natural course of LSS in patients without planned surgical treatment. A range of clinical and radiological data are collected at defined time points. To administer, guide, monitor and assist the surgical units and the researchers involved, the NORDSTEN national project organization was established.

Corresponding clinical data from the Norwegian Registry for Spine Surgery (NORspine) were used to assess if the randomized NORDSTEN-population at baseline was representative for LSS patients treated in routine surgical practice.

Results A total of 988 LSS patients with or without spondylolistheses were included from 2014 to 2018. The clinical trials did not find any difference in the efficacy of the surgical methods evaluated. The NORDSTEN patients were similar to those being consecutively operated at the same hospitals and reported to the NORspine during the same time period.

Conclusion The NORDSTEN study provides opportunity to investigate clinical course of LSS with or without surgical interventions. The NORDSTEN-study population were similar to LSS patients treated in routine surgical practice, supporting the external validity of previously published results.

Trial registration ClinicalTrials.gov; NCT02007083 10/12/2013, NCT02051374 31/01/2014 and NCT03562936 20/06/2018.

Keywords Lumbar spinal stenosis · Degenerative spondylolisthesis · NORDSTEN organization · Randomized multicentre study · Observational cohort

Abbreviations

ASA	American society of anesthesiologists classification
CRF	Case report forms
DA	Decompression alone
DF	Decompression with instrumental fusion
DS	Degenerative spondylolisthesis trial
FORMI	Research and communication unit for musculoskeletal health
GCP	Good clinical practice
LSS	Lumbar spinal stenosis
NORDSTEN	Norwegian Degenerative spondylolisthesis and spinal stenosis study
NORspine	Norwegian Registry for Spine Surgery
NRS	Numeric rating scale
OC	Observational cohort
ODI	Oswestry disability index
PI	Principal investigator
PROM	Patient reported outcome measures
SST	Spinal stenosis trial

Extended author information available on the last page of the article

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Background

Lumbar spinal stenosis (LSS) is the most common indication for spine surgery in the age group above 65, and the rates of LSS surgery are increasing [1–3]. Patients with mild to moderate symptoms may have satisfactory long-term outcomes without surgical treatment [4, 5], but prospective long-term observational studies are scarce.

The main objective of the surgical treatment for LSS is to decompress neural structures to alleviate pain and improve function. There are several surgical decompression techniques available, but evidence for recommending one technique over the other is limited [6]. In the USA and Australia, the use of complex fusion has increased greatly [3, 7], even if these procedures are more costly and may put patients at risk for more serious complications [3, 7, 8]. Adding fusion surgery to the decompression in cases with LSS and degenerative spondylolisthesis (DS), is controversial issue in spine surgery.

Hence, The Norwegian Degenerative spondylolisthesis and spinal stenosis (NORDSTEN) study, a large nationwide multicentre study with a 10 year follow-up, was initiated to generate more evidence to improve management of LSS. NORDSTEN consists of the following main studies:

A. In the spinal stenosis trial (NORDSTEN-SST) patients were randomized to three different decompression techniques: spinous process osteotomy, bilateral laminotomy and unilateral laminotomy with crossover [9].

B. In the degenerative spondylolisthesis trial (NORDSTEN-DS) patients with LSS and concurrent degenerative spondylolisthesis were randomized to surgical decompression alone (DA) or decompression with instrumental fusion (DF) [10].

C. In the observational cohort (NORDSTEN-OC) we followed the patients with radiographic and symptomatic LSS with and without DS, who had symptom burden judged not severe enough to opt for surgical treatment.

Crucial for the external validity is that patients included are representative of those not included in this study, i.e., those receiving the standard package of care, according to surgeons and patients' preferences. Information on these patients is recorded in the Norwegian Registry for Spine Surgery (NORspine).

The main purpose of the present paper is to give an overview of the NORDSTEN study, to present the study organization and to evaluate if the surgically treated NORDSTEN-study population is similar to patients reported to the National Registry for Spine Surgery (NORspine).

Methods

Study governance and organization

In order to govern, guide and follow-up all aspect of the NORDSTEN study, a national project organization was established (Fig. 1).

Biannual meetings/conferences with the scientific board, administrative executive board, working group, patient representative, study monitor and the study coordination center were arranged to ensure adherence to the study protocol and to inform about the progress of the study.

Study population

Patients with symptomatic LSS referred to orthopedic or neurosurgical outpatient clinics at public hospitals were eligible to the study. Inclusion and exclusion criteria are listed in Table 1, and detailed in protocol articles [9, 10].

Patients were offered participation in one of the three studies (Fig. 2).

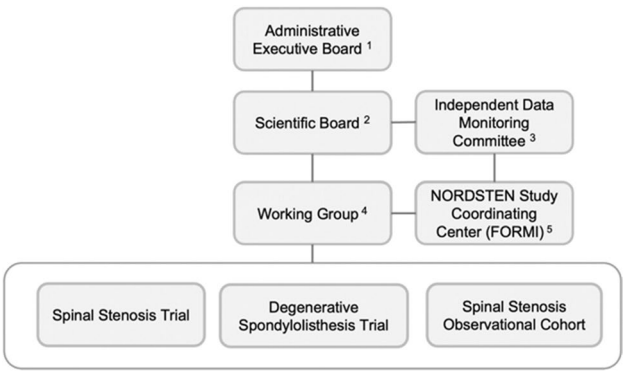

Fig. 1 The Norwegian Degenerative spondylolisthesis and spinal stenosis (NORDSTEN) organization. 1. Members: head of the NORDSTEN study, head of scientific board, investigators for each study, head of NORDSTEN coordinating center and head of finances. 2. Members: all Administrative Executive Board members, principal investigators (PIs) from all four health regions in Norway, an international researcher and a patient representative. 3. An independent data monitoring committee at Clinical Trial Unit (CTU) at Oslo University Hospital (OUH). 4. Members: local PIs (surgeons) and study coordinator from each of the recruiting hospitals, and staff from the national NORDSTEN coordinating center. Responsibilities: recruit, treat and follow-up of patients in accordance with the standard procedures and guidelines developed by the Scientific Board and the Administrative Executive Board. Also, an external study monitor supervising activities according to Good Clinical Practice. 5. The Research and Communication Unit for Musculoskeletal Health (FORMI) at OUH is responsible for the nationwide coordination of the NORDSTEN study. Responsible for daily administration and support to the local coordinators, the randomization process and data management (collection and recording). Reports to the independent data monitoring committee at CTU/OUH

Table 1 Inclusion and exclusion criteria for the NORDSTEN study separated for the spinal stenosis trial (SST), the degenerative spondylolisthesis study (DS) and the observation cohort (OC)

Inclusion criteria of NORDSTEN	SST	DS	OC
Men and women, age > 18, ≤ 80 years	√	√	√
Clinical symptoms of LSS (defined as neurogenic claudication or radiating pain into the lower limbs (in SST, bilateral symptoms were required))	√	√	√
Not responding to at least 3 months of nonsurgical treatment	√	√	√
Radiological findings corresponding to the clinical symptoms: central, lateral recess or foraminal stenosis	√	√	√
Understanding Norwegian language, spoken and written	√	√	√
Able to give informed consent and able to comply with the protocol	√	√	√
DS with a slip ≥ 3 mm verified on upright, lateral view X-ray		√	
Spinal stenosis at the level of spondylolisthesis, verified on MRI		√	
Exclusion criteria of NORDSTEN			
Former surgery at the level of stenosis	√	√	√
Former fracture or fusion of the thoraco-lumbar spine	√	√	√
Cauda equina syndrome (bowel or bladder dysfunction) or fixed complete motor deficit	√	√	√
ASA grade 4 or 5[&]	√	√	√
Lumbosacral scoliosis > 20°, measured on upright front-view X-ray	√	√	√
Distinct symptoms in lower limbs due to other diseases such as polyneuropathy, vascular claudication or osteoarthritis	√	√	√
Stenosis in more than three lumbar levels	√	√	√
Not able to comply fully with the protocol, including treatment, follow-up or study procedures	√	√	√
Participating in another clinical trial that may interfere with the present trial	√	√	√
ODI score < 25[§]	√	√	
DS with a slip ≥ 3 mm verified on upright, lateral view X-ray	√		
Presence of isthmic defect in pars inter-articularis		√	
Radicular pain due to a foraminal stenosis grade 3 at the slipped level with deformation of the nerve root because of a bony narrowing in the vertical direction, verified by MRI[#]		√	
Spondylolisthesis at more than one level		√	

& An American Society of Anesthesiologists (ASA) 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 h without surgery

§ From February 12, 2014 (start of inclusion) to August 29, 2015, a score below 25 on the Oswestry Disability Index was an exclusion criterion

[#] Grade 3 according to Lee Classification [11]

Inclusion started in February 2014 and ended in October 2018, and baseline data for the current analysis were available when 2 year follow-up was completed.

Study interventions and randomization

Shared decision-making between surgeon and patient determined if surgical or nonsurgical treatment would be implemented. If opted for surgery, patients were eligible for the randomized trials, if not; they were eligible for the OC. Surgical interventions used in NORDSTEN are documented in detail in protocol articles [9, 10] and shown in short in Table 2.

All participating surgeons were experienced with the treatments used in the trials. Prior the start of the trials, principal investigators (PIs) from the Scientific Board visited the hospitals to ensure a common understanding and performance of the surgical methods described in study protocols.

Randomization in the two interventional trials was carried out within a 6 week period prior to surgery. Randomization lists were computer generated, center-stratified and block permuted with a 1:1:1 (SST trial) or 1:1 (DS trial) allocation and performed within the Medinsight database (version 2.17.9), a research database developed and owned by Oslo University Hospital.

Data collection and monitoring

Data are/were collected preoperatively (baseline), and at 3 months, 1, 2, 5 and 10 year postoperatively (Fig. 3). Data are/were collected in collaboration between local coordinators and NORDSTEN-study coordinating center (FORMI).

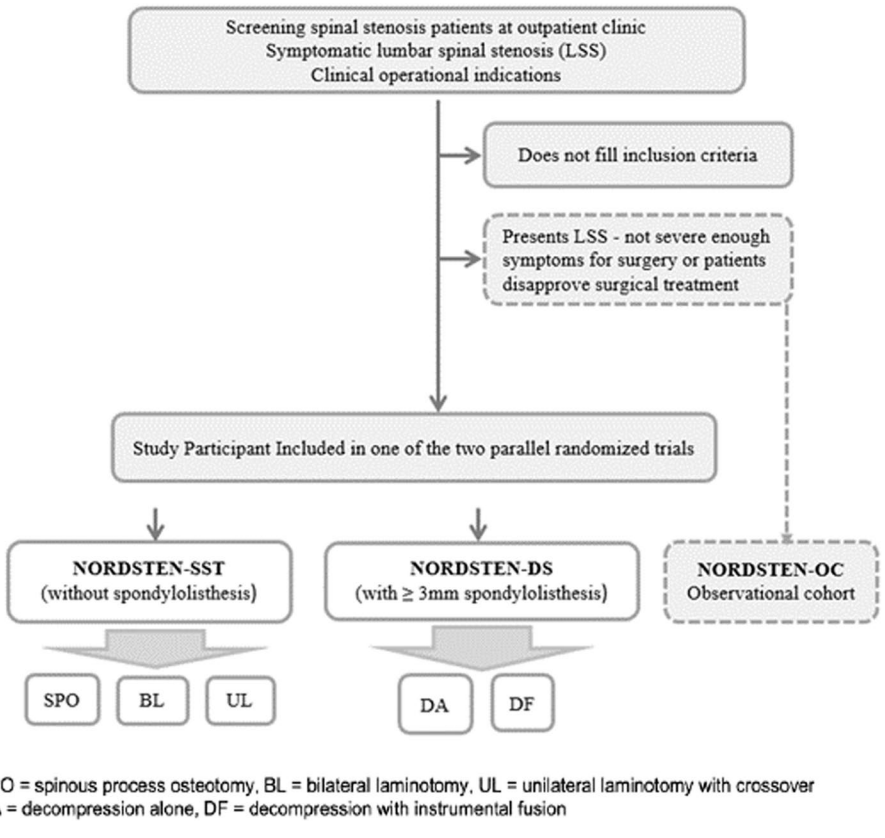

Fig. 2 Participation of patients in the NORDSTEN study. Flow chart of The Norwegian Degenerative spondylolisthesis and spinal stenosis (NORDSTEN) study displaying the four potential outcomes after screening patient at the outpatient clinic at 18 Norwegian public hospitals: 1) patient did not fill inclusion criteria or filled exclusion criteria—excluded, 2) patient not opted for surgical treatment—observation cohort (OC), 3) patient had indication for surgery (without spondylolisthesis)—the spinal stenosis trial (SST), and 4) patient had indication for surgery (with spondylolisthesis)—the degenerative spondylolisthesis trial (DS)

FORMI, the Clinical Trials Unit (CTU) at Oslo University Hospital and the external study monitor are responsible for data safety and quality. The data control plan included automatic and manual checks of data quality at defined time intervals. Plotting of primary outcome was verified for all research subjects at all follow-up intervals, all other data entered were verified for every fifth research participant number (20%). In addition, an agreement outlined a database lock until 2 year follow-up was completed, and how data were made available.

As an intervention study it was decided to implement the Good Clinical Practice (GCP) guidelines in the NORDSTEN-SST and -DS trials in order to add quality, increase resource efficiency and safety [12]. The external study monitor visited study sites regularly throughout the first 2 year follow-up (Table 3), and reviewed all included patients regarding deviations from the protocol.

All scientific board members, PIs, local study coordinators and staff at the NORDSTEN-study coordinating center underwent GCP certification course prior to study commencement.

Study variables

The present paper presents baseline data collected both in the NORDSTEN study and in the NORspine registry: 1) descriptive baseline characteristics (age, gender, level of education, work status, smoking habits, marital status, duration of back pain history, former back surgery and American Society of Anesthesiologists classification (ASA); 2) the Norwegian validated version of Oswestry Disability Index (ODI) version 2.0 [13] as the primary outcome measure; and 3) Numeric Rating Scale (NRS) for back and leg pain, EuroQol 5 dimensions questionnaire (EQ-5D) as secondary outcome measures.

In the NORDSTEN study some variables specific for patients with LSS were added: the Norwegian validated version of the Zürich Claudication Questionnaire (ZCQ) and the Hopkins symptom check list (emotional distress) [9, 10]. A range of radiological measurements were performed in all NORDSTEN studies. Case report forms (CRF's) for registration of adverse events were designed [12]. All data were collected by paper. At hospital admission, patients completed questionnaires, which included patient reported outcome measures (PROMs) and questions about demographics and lifestyle. The surgeons recorded surgical parameters.

The local coordinators (not involved in the treatment) reported complications/adverse events (including reoperations) in CRFs. The external monitor cross-checked all reported data in the CRF's against clinical patient journal. In the present paper, monitoring report is only reported preoperatively.

Table 2 Short presentation of the surgical interventions used in the NORDSTEN study. All operations performed through posterior approach and with use of microsurgical principles

Trial	Surgical intervention	Description
Spinal stenosis trial (SST)	Unilateral laminotomy with crossover	Midline structures preserved Decompression ipsilaterally and then contralaterally
	Bilateral laminotomy	Midline structures preserved Decompression performed on both sides
	Spinous process osteotomy	Osteotomy at the base of the spinous process above (and sometimes under) the affected level. Supraspinal and interspinal ligaments intact Decompression in midline and laterally on both sides
Degenerative spondylolisthesis trial (DS)	Decompression alone	Midline structures preserved Method of decompression surgeon's choice
	Decompression and instrumental fusion	Method of decompression surgeon's choice. Posterolateral pedicle screw fixation. ± cage

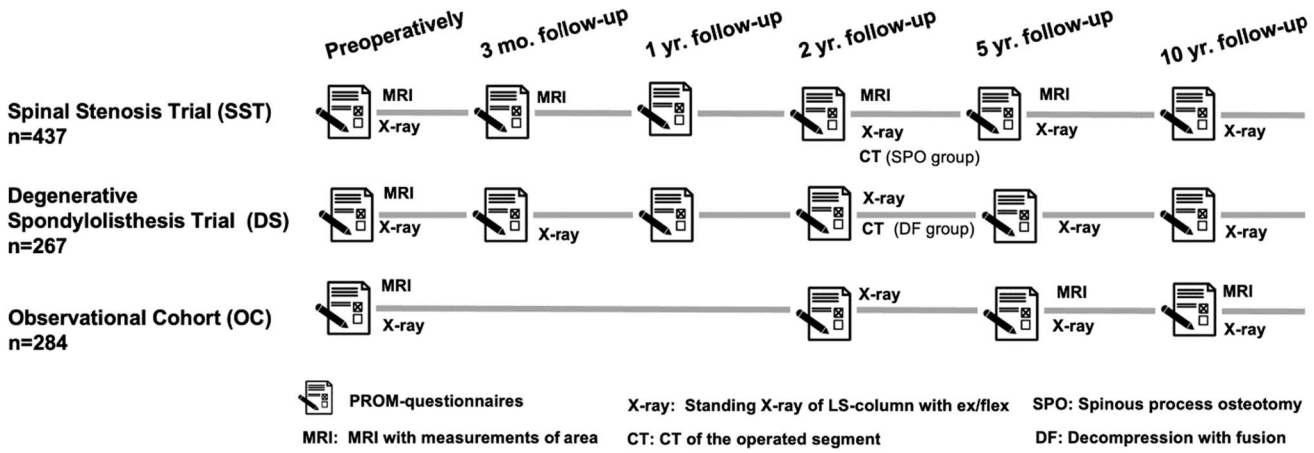

Fig. 3 Timeline for the data collection in the NORDSTEN study. The data collection process throughout the 10 years follow-up period for the The Norwegian Degenerative spondylolisthesis and spinal stenosis (NORDSTEN) study

Radiological evaluations in NORDSTEN: standing X-ray with functional images and standard MRI of the lumbar spine, including T1 and T2 sequences in the axial and sagittal planes were performed on all patients at baseline. See Fig. 3 for radiological follow-ups.

Study design and statistical analysis

Main endpoint for the NORDSTEN-SST and NORDSTEN-DS is at 2 year follow-up, and for NORDSTEN-OC at 5 year follow-up.

Table 3 Participating hospitals (study sites) in the NORDSTEN study with number of patients (study participants) in the spinal stenosis trial (SST), the degenerative spondylolisthesis study (DS) and the observation cohort (OC). The number of monitoring visits was performed according to number of patients enrolled at the study sites

Study sites	Study participants (n)			Monitoring visits (n)
	SST	DS	OC	
Oslo University Hospital, Orthopedic dept	36	25	3	4
Akershus University Hospital, Orthopedic dept	24	12	5	2
Bærum Hospital, Orthopedic dept	28	11	39	4
Skien Hospital, Orthopedic dept	17	12	0	2
Arendal Hospital, Orthopedic dept	21	7	6	3
Gjøvik Hospital, Orthopedic dept	39	12	11	4
Lillehammer Hospital, Orthopedic dept	15	2	4	2
Stavanger University Hospital, orthopedic dept. and dept. of Neurosurgery	57	42	36	3
Haukeland University Hospital, Orthopedic dept. and dept. of Neruosurgery	5	21	25	6
Kysthospitalet i Hagevik, Haukeland University Hospital, Orthopedic dept	61	78	93	4
Ålesund Hospital, Orthopedic dept	61	24	44	4
St. Olav University Hospital, dept. of Nerurosurgery	0	4	2	1
University Hospital of Northern Norway, dept. of Neurosurgery	6	14	1	3
Kristiansand Hospital, Orthopedic dept	5	1	0	1
Elverum Hospital, Orthopedic dept	1	2	5	1
Levanger Hospital, Orthopedic dept	28	0	0	3
Martina Hansen Hospital, Orthopedic dept	30	0	9	3
Drammen Hospital, Orthopedic dept	3	0	0	0

The SST trial is a superiority trial comparing three surgical decompression techniques [9]. The DS trial is a non-inferiority trial comparing DA and DF [10]. The reporting of the two randomized trials follows CONSORT (Consolidated Standards of Reporting Trials) checklists for reporting randomized trials. For the OC study, STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines will be used. A statistician, blinded to treatment allocation, conducted the statistical evaluations of main outcomes in the two randomized NORDSTEN trials. Statistical analysis plans were published before data were made accessible.

Representativeness of the NORDSTEN-study population

To evaluate if the patients enrolled in the NORDSTEN study were similar to patients operated in an ordinary clinical setting in Norway, baseline data from the NORspine, a national quality registry for surgical treatment for degenerative disorders in the cervical and lumbar spine, were used. Preoperative data registered in NORspine from the same hospitals on corresponding patient groups treated consecutively in the same period were used to describe baseline characteristic of those not included in NORDSTEN study.

Descriptive comparison between patients included in the two NORDSTEN randomized trials and patients reported in the NORspine registry was done without direct statistical comparison as the intention was to judge if the patient populations were similar.

Results

The 18 recruiting hospitals (19 study sites) were both university hospitals and smaller public hospitals located in all regions of Norway (Table 3). In total 2227 patients were screened for eligibility at outpatient clinics between February 2014 and September 2018 (Fig. 4). Seven hundred and four (32%) were included and operated for LSS with or without spondylolistheses in the randomized NORDSTEN trials (267 + 437), whereas 284 patients were included in the observation cohort. Mean time from randomization to surgery was 12.4 (SD 21.9) and 16.9 (SD 22.4) days in the SST- and DS trial, respectively. The number of patients reported to the NORspine registry from the same hospitals, the same time period and with the same inclusion/exclusion criteria as in the NORDSTEN study was 2908 of 4310 (67%). This means that about 1 of 5 of available patients (704/3612) from the participating hospitals were included in the randomized NORDSTEN trials.

Baseline characteristics of the NORDSTEN and the NORspine cohorts are shown in Table 4. Only minor differences were registered between patients included in the randomized NORDSTEN trials and other patients

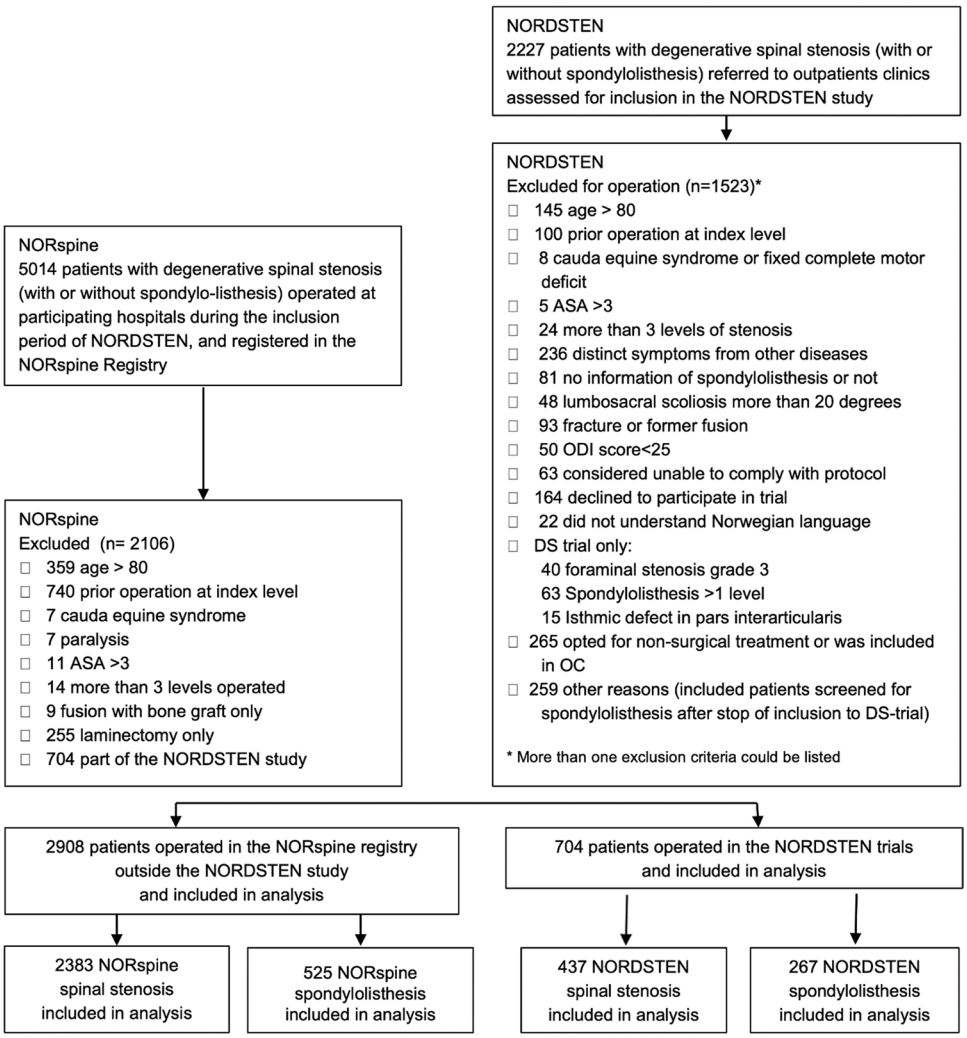

Fig. 4 Patient selection in in the NORspine registry and the NORDSTEN study. Flow chart of the Norwegian Registry for Spine Surgery (NORspine) and The Norwegian Degenerative spondylolisthesis and spinal stenosis (NORDSTEN) study. Patients from the NORspine were selected by the same inclusion and exclusion criteria as in NORDSTEN

operated at the 18 participating hospitals and reported to the NORspine registry in the same period.

Monitoring the NORDSTEN study detected deviations (Table 5). Most of them were minor (i.e., radiology and PROMs completed out of set time period, informed consent not signed correctly).

Brief results from NORDSTEN papers 2 years postoperatively

NORDSTEN-SST reported no differences in clinical outcomes or complication rates among the 3 minimally invasive posterior decompression techniques used to treat patients with lumbar spinal stenosis [15]. NORDSTEN-DS found that in patients operated for degenerative lumbar spondylolisthesis decompression was noninferior to decompression with instrumented fusion [14].

Discussion

The NORDSTEN study is an ongoing multicentre study including 988 patients suffering from LSS with or without degenerative spondylolisthesis recruited over a period of 4.5 years. The aim of NORDSTEN study is primarily to evaluate the efficacy of different surgical methods for treating patients with LSS. The comprehensive organization of the NORDSTEN study is considered to ensure high quality and control in the planning process, patient recruitment and treatment and follow-up phases.

Planning

Large resources were used in the planning phase of the NORDSTEN study to ensure open discussions carried out in the formation of the research protocols [9, 10].

Table 4 LSS patients included in the NORspine registry and in the NORDSTEN trials. Comparing patients included in The Norwegian Degenerative spondylolisthesis and spinal stenosis (NORDSTEN) study with the patients registered in the Norwegian Registry for Spine Surgery (NORspine). Patients were operated in the same hospitals, in the same time period and with the same diagnosis. There were some missing data; completeness varied between 92 and 100% from the NORDSTEN study and 93–100% from the NORspine register

	NORspine ($n=2908$)	NORDSTEN ($n=704$)
Demographical characteristics		
Age (years)		
Median (min–max)	67 (26–80)	68 (33–80)
< 50; *n* (%)	251 (8.6%)	23 (3.3%)
50–69; *n* (%)	1524 (52.4%)	398 (56.5%)
70–80; *n* (%)	1133 (39.0%)	283 (40.2%)
Female gender; no (%)	1590 (54.7%)	389 (55.3%)
Education; no (%)		
Primary school or high school	726 (25.4%)	181 (26.8%)
> 4 years higher education	377 (13.2%)	82 (12.1%)
Working status; no (%)		
Working	381 (13.4%)	105 (15.4%)
Age pension	1382 (48.5%)	364 (53.3%)
Sick leave / rehabilitation	620 (21.8%)	124 (18.1%)
Disability benefits	476 (16.7%)	91 (13.1%)
Others	86 (3.0%)	14 (2.0%)
Norwegian first language; no (%)	2725 (94.1%)	664 (97.6%)
General health		
EQ-5D VAS[$] (mean ± SD)	46.8 (19.9)	48.4 (19.3)
BMI* *(mean ± SD)*	27.9 (4.5)	27.8 (4.3)
Smoker; no (%)	568 (19.7%)	132 (19.4%)
ASA score[£]; no (%)		
I	290 (10.0%)	76 (11.4%)
II	1935 (66.9%)	467 (70.0%)
III	668 (23.1%)	124 (18.6%)
Spinal symptoms and clinical scores		
Duration of leg pain ($n>1$ year duration/no (%))	1851 (67.3%)	460 (71.0%)
Duration of back pain ($n>1$ year duration/no (%))	2169 (77.9%)	540 (80.7%)
Use of analgetics (% yes)	2381 (82.9%)	521 (77.2%)
ODI (mean ± SD)[&]	40.0 (15.3)	38.8 (14.0)
NRS—leg pain (mean ± SD)[#]	6.5 (2.3)	6.5 (2.0)
NRS—back pain (mean ± SD)[#]	6.6 (2.1)	6.5 (2.1)
EQ-5D-3L (mean ± SD)[¤]	0.36 (0.32)	0.39 (0.31)

$ EuroQol Group 5-Dimension (EQ-5D) visual analouge scale (VAS); range 0–100, where 100 represent better health-related quality of life, * Body Mass Index; the weight in kilograms divided by the square of the height in meters, £ American Society of Anesthesiologists (ASA) score I indicates no disease, II mild systemic disease, and III severe systemic disease that is not life-threatening, & Oswestry Disability Index (ODI); range 0 to 100, where 100 represent greatest impairment, # Numeric Rating Scale (NRS); range 0–10, higher scores indicating more pain, ¤ The 3-level version of the EuroQ ol Group 5-Dimension (EQ-5D-3L); range −0.59–1.0, higherscores indicating better health-related quality of life

The decision to prospectively follow disease progress of included patients by PROMs and radiological imaging during the 10 years of follow-up creates a unique opportunity to improve knowledge and routines related to clinical practice, and increased precision implementation of imaging and surgical procedures.

It is of outmost importance to ensure that the patients enrolled in the randomized trials are representative to patients treated in routine surgical practice. The inclusion and exclusion criteria were set to allow for generalization to the majority of patients with LSS evaluated for surgical treatment. External validity was therefore controlled by comparison of the NORspine registry once the database lock was suspended in adherence with the data security plan (completion of 2 year follow-up for SST and DS trials).

Table 5 GCP deviations until hospital admission in the NORDSTEN study. Deviations until hospital admission according to GCP monitoring The Norwegian Degenerative spondylolisthesis and spinal stenosis (NORDSTEN) study. Grade 1: no impact on data quality or patient safety, Grade 2: minor impact on data quality, Grade 3: minor impact on patient safety. Grade 4 (major impact on data quality or patient safety) and Grade 5 (participating leading to patient serious adverse event and/or death) are described in the papers reporting main clinical results of the SST and DS trials [14, 15]

		Number
Grade 1	Incomplete delegation log and CV, copy of regulative approval (per included center)	14
Grade 2	Preoperative radiological examination taken out of time range[#]	91
	Preoperative PROMs completed out of time range [&]	10
Grade 3	Incomplete signed informed consent process (e.g., missing date/signature from either patient/surgeon/study coordinator, patient/surgeon/study coordinator signed post randomization, wrong informed consent signed)	56

Set time was less than 6 months before surgery, numbers include both MRI and X-ray, & PROMs should be completed at admission for surgery

Strengths and limitations

Standardization of surgical procedures is challenging, but measures were taken to harmonize the execution of the surgical interventions at the eighteen hospitals. However, the design of the NORDSTEN study was also pragmatic in giving surgeons choice regarding surgical methods and instrumentation [9, 10]. The NORDSTEN randomized trials were not planned with control groups (e.g., sham surgery) and were not designed to evaluate the placebo effect. Neither were the patients blinded for treatment allocation.

As part of the shared decision-making regarding treatment, patients should be informed about the present evidence of the efficacy of surgery. Inclusion of patients in the NORDSTEN trials was conducted by spine surgeons. According to a Cochrane report, high quality research is needed in order to conclude about the benefits of surgical versus nonsurgical treatment [16]. Therefore, it is a limitation that the NORDSTEN did not include nonsurgical treatment as an arm in the study. The observation cohort in NORDSTEN is a selective cohort and cannot be applied to evaluate the natural course of LSS in general; however, it can tell the story of patients with LSS referred for surgery not operated.

The importance of the patient's perspective in the evaluation of treatment has been generally recognized, and several types of patient-based outcome measures have been developed. The use of PROMs translated and validated for the Norwegian population and recommended by international panels of experts [17] ensured valid results and conclusions. The ODI was chosen as the primary outcome because it is the most commonly used back-specific measure that has been found reliable and valid despite that ODI was primarily designed to evaluate back pain. The less frequently used Zurich Claudication Questionnaire (ZCQ) was added due to the instruments specificity regarding the evaluation of function for LSS populations [18]. Standardized and well documented methods were used for data collection and analysis, and all main analyses are performed by statisticians blinded for treatment allocation.

The study organization, responsibilities and tasks were carefully planned in the early phase to ensure a good completion of the study. We have experienced that our research network has been robust with dedicated people at all levels which has been decisive for the results.

Standardized routines for study hospitals, study personnel and study coordinating center along with close collaboration between all trials organizations could be a contributing factor to the low dropout rates. In addition, informational letters regarding study progression and layman summaries have been sent out to study patients in collaboration with the study's patient representative.

The uneven recruitment of patients to the SST and DS studies versus the OC study, is primarily due to the organization and routines at the different hospitals. At some university hospitals, many of the patients were first evaluated at departments of physical medicine, where physicians often were less involved in the NORDSTEN study. If surgery was considered a possible choice of treatment, patients were referred to an orthopedic/neurosurgical department for further consultation. Due to this practice many patients were not screened or included in the OC study.

External validity

NORDSTEN recruited a higher proportion of patients and hospitals than, e.g., the SPORT study [16, 17] and to our knowledge, any other former published randomized LSS trials. In addition, dropout rates have been very low; both at 2 years postoperatively (90%) and indications for 5 years postoperatively (> 80%).

The duration of symptoms for patients operated in the NORDSTEN study was greater than 1 year for the majority of patients (leg/back pain: 71%/81%), considerably higher

than in the SPORT study where only about one third had symptoms for greater than 1 year [16]. The Scandinavian tradition is to let patients recover through natural course via nonsurgical treatment and offer those who do not benefit surgery. Therefore, our population varies somewhat from the population reported in the SPORT trials; however, the change in ODI from baseline to 2 year follow-up is comparable to the SPORT study [14, 15, 17, 18]. The high proportion of female patients operated for DS was in accordance with other studies [16, 19, 20].

Ideally, all consecutive eligible patients should have been enrolled in the NORDSTEN study. Since this was not the case, a corresponding patient population from the NORspine registry provided useful additional information about those not included. The NORspine national coverage rate at institutional and individual level varies throughout the years and hospitals. The report from 2019 stated a coverage rate of 95% at the institutional level and 69% at the individual level for lumbar spine surgery [21]. Dropout analysis showed that patients who were not reported to the registry, were mainly emergency patients. The coverage rate for planned surgery was nearly twice as high as for emergency surgery [21]. Therefore, the LSS patients operated and reported to the registry should be representative for the typical LSS patients treated by surgery in Norway, and suitable for comparison with the NORDSTEN-study population. The patients in the NORDSTEN study and the NORspine registry were similar at baseline indicating that results from the NORDSTEN study may be generalized to the broader population. Although a large study population alone cannot exclude selection bias the pragmatic nature of NORDSTEN may also generate evidence generalizable to routine practice.

Even though the patients enrolled in the NORDSTEN study were found to be representative for the Norwegian surgical LSS-population, this may not be the case elsewhere. However, the population characteristics of NORspine have been found to be similar in other Scandinavian countries [22], and also comparable to LSS populations in USA [23]. Baseline demographical data in the two randomized NORDSTEN trials are in accordance with former studies both regarding age, gender, body mass index, ODI score, leg pain and health-related quality of life [16, 17, 19, 20].

Feasibility

Several factors potentially contributed to the feasibility of this triple designed, multicenter study with complex protocols. With several study hospitals and multiple study personnel involved, communication was at the forefront of the design. There was a common agreement on the importance of achieving a higher level of scientific evidence to guide clinical decisions that may have been vital in the present project. In addition, study hospitals were supported in the adaption of the study's procedures to their local routines through initiation meetings. The biannual meetings held throughout the study period for all study governance groups encouraged dialog and sharing of experiences between all groups which had an important sub goal; to achieve a sense of ownership to the project throughout all organizational levels. In addition, all regional PIs were represented on the scientific board contributing to effective dissemination of information within the study network. Another potential beneficial factor contributing to the high and timely recruitment rate, may be the parallel recruitment in all three trials.

The implementation of GCP ensured an ethical and scientific quality of data collection and patient follow-up, even though also contributing to increasing trial complexity and costs [24].

The NORDSTEN study applied for and has been granted public financial support from the health authorities that gave the possibility to implement this large multicenter study independently.

The Norwegian health care system is founded on the principle of universal access regardless of differences in socioeconomic status and place of living. The responsibility for provision of health care is decentralized. Differences in health care systems could influence the choice of treatment of LSS patients and spine surgery compared to countries with higher share of nonpublic health services and hospitals primarily funded by private insurance. The Norwegian national identity number provides the opportunity to follow-up patients nationwide.

Future plans for the NORDSTEN study

The NORDSTEN 5 year follow-up ends in 2023 and 10 year in 2028, and several publications are planned regarding both clinical and radiological outcomes of these LSS patients treated surgically or nonsurgically. The high follow-up rate provides a good base for further and deeper investigations into the clinical and radiological outcomes. Other publications alongside the main study results are among others planned regarding predictor analysis, methodological analysis and cost analysis.

Conclusion

The NORDSTEN study provide important evidence regarding surgical and nonsurgical treatment of patients with LSS. Baseline data from the NORspine registry suggests that patients enrolled in the NORDSTEN study are similar to LSS patients treated in routine surgical practice.

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Author contributions KI, EH, IMA, FR, TKS, JIB, CH and KS contributed to the planning of the study; IFB and MHG contributed to collect the data; KI, IFB and KS analyzed the results, interpreted the results and wrote the draft of the manuscript. All authors contributed to revision of the draft and approved the final version to be published.

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Availability of data and materials The datasets generated during the current study are available from the corresponding author on reasonable request. Medical researchers's request has to be in accordance with local registration and ethical approval, and datasets will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. All proposals requesting data access will need approval of the scientific board before any data can be released.

Declarations

Conflict of interest The authors have no relevant financial or nonfinancial interest to disclose.

Ethics approval The Norwegian Committees for Medical and Health Research Ethics approved the trials (NORDTEN-SST trial and NORDSTEN-OC; 2011/2034, NORDSTEN-DS trial; 2013/366). Data protection was approved by the Norwegian Data Inspectorate and data are stored at "Services for sensitive data" (TSD) hosted by the University of Oslo, to allow secure data sharing between researchers. The study was performed according to the Helsinki Declaration and registered at ClinicalTrials.gov under the following identifiers; SST: NCT02007083 10/12/2013 / DS: NCT02051374 31/01/2014/OC: NCT03562936 20/06/2018. The trial is monitored according to requirements of the Good Clinical Practice (GCP) guidelines.

Consent to participate Informed consent was obtained from patients included in the study after oral and written information.

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