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The European Robotic Spinal Instrumentation (EUROSPIN) study: Design of a multicenter pragmatic controlled trial of pedicle screw revision in robot-guided, navigated, and freehand thoracolumbar fusion surgery

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Competing Interests

JFCW reports a consultancies for Safe Orthopaedics, Zimmer-Biomet, Silony, and EIT. FH reports a consultancy for Evospine. ML reports a consultancy for Zimmer-Biomet Robotics. SMK reports consultancies for Nexstim, Brainlab, and Spineart Deutschland, and has received honoraria from Medtronic and Carl Zeiss Meditec. BM reports consultancies for Medtronic, Brainlab, and DePuy Synthes. PPG reports a consultancy for DePuy Synthes. CT reports receiving research supports and honoraria from DePuy Synthes, Icotec, Medtronic Intrinsic Therapeutics, Signus Medical, Brainlab, and Pfizer. ET reports consultancies for DePuy Synthes, Spineart, Medtronic, and Brainlab. All other authors declare that the protocol and its content were composed in the absence of any commercial or financial relationships that could be construed as a potential competing interest.

Author Contributions

VES, GM, PMvK, ET, MLS conceived and designed the study. VES, PMvK, JWRT conceived the statistical analysis plan. VES, GM, PMvK, ET, MLS prepared the first draft of the study protocol. All authors contributed to the final design of this study protocol. All Authors critically revised the manuscript. All Authors approved the final version of the manuscript and agree to be accountable for the accuracy of the work. MLS supervised the work and is the guarantor.

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Study Sponsor and Principal Investigator

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Abstract

Introduction

Robotic guidance (RG) and computer-assisted navigation (NV) have seen increased adoption in instrumented spine surgery over the past decade. Although there exists some evidence that these techniques increase radiological pedicle screw accuracy compared to conventional freehand (FH) surgery, this may not directly translate to any tangible clinical benefits, especially considering the relatively high inherent costs. As a non-randomized, expertise-based trial, the European Robotic Spinal Instrumentation (EUROSPIN) Study aims to create prospective multicenter evidence on the potential comparative clinical benefits of RG, NV, and FH in a real-world setting.

Methods and Analysis

Patients will be allocated in a non-randomized, non-blinded fashion to the RG, NV, or FH arms. Adult patients that are to undergo thoracolumbar pedicle screw instrumentation for degenerative pathologies, infections, vertebral tumors, or fractures will be considered for inclusion. Deformity correction and surgery at more than 5 levels represent exclusion criteria. Follow-up will take place at 6 weeks, as well as 12 and 24 months. The primary endpoint was defined as the time to revision surgery for a malpositioned or loosened pedicle screw within the first postoperative year. Secondary endpoints include patient-reported back and leg pain, as well as Oswestry Disability Index and EQ-5D questionnaires. Use of analgesic medication and work status will be recorded. The primary analysis, conducted on the 12-month data, will be carried out according to the intention-to-treat principle. The primary endpoint will be analysed using crude and adjusted Cox proportional hazards models. Patient-reported outcomes will be analysed using baseline-adjusted linear mixed models. The study will be monitored according to a pre-specified monitoring plan.

Ethics and Dissemination

The study protocol is approved by the appropriate national and local authorities. Written informed consent will be obtained from participants. The final results will be published in an international peer-reviewed journal.

Trial Registration Number

NCT03398915; Pre-results, recruiting stage

Strengths and Limitations of this Study

- Large, pragmatic, controlled trial carried out in thirteen pan-European centers
- Long-term, 2-year follow-up with standardised and validated patient-reported outcomes
- Expertise-based controlled trial design
- Even with adjusted analyses, lack of randomization may constitute a bias
- Potential performance bias due to lack of blinding of surgeons and patients

Introduction

In the Unites States alone, an estimated 3.6 million spinal instrumentations were performed between 2001 and 2010, with more than $287 billion in total charges created, and an increasing trend.[1] In 2013, only 11% of spine surgeons routinely used navigation systems.[2] Meanwhile, more and more surgeons are implementing computer assistance into their clinical practice, one reason being the adoption of minimally invasive (MI) techniques, further increasing the need for navigation due to often inexistent line-of-sight.[2,3]

In 1995, the concept of computer-assisted navigation was introduced to spine surgery.[4] Modern navigation systems (NV) assist in pedicle screw insertion by projecting screw trajectories onto pre- or intraoperatively obtained and co-registered computed tomography (CT) or 3D-fluoroscopic (3DFL) images.[5] Robotic guidance (RG), introduced in 2006, takes one further step by providing mechanical guidance according to pre-planned screw trajectories, eliminating the need of on-the-spot establishment of trajectories by the surgeon. These systems can be considered cooperative robots ("cobots"), since they do not insert screws autonomously, rather providing stable guidance.[6]

While there is some evidence that RG and NV lead to higher radiological accuracy than freehand (FH) instrumentation [7–13], this may not translate directly to real-world clinical benefits, especially in light of the high acquisition and maintenance costs inherent to these systems. Possible benefits could include shorter operating times, and decreased incidences of radiculopathy and costly revision surgery for screw malposition, although the current level of evidence is very low.[5,11,14–22]

Currently, few published studies compare these techniques in a prospective setting, although they often suffer from insufficient power to demonstrate any potential clinical benefits, or report major conflicts of interests. Furthermore, while many studies compare RG to FH, there are no powerful studies comparing RG and NV.[5] We aim to conduct a prospective controlled trial comparing RG, NV, and FH to create unbiased real-world evidence on these instrumentation techniques.[23]

Methods and Analysis

Study Design

The European Robotic Spinal Instrumentation (EUROSPIN) study is a prospective, international, multicentre, pragmatic, open-label, non-randomized controlled trial comparing the effectiveness of three techniques for pedicle screw instrumentation, namely RG, NV (CT-, O-Arm, or 3DFL-based), and FH.[23–25] Following the baseline evaluation, patients will receive one of the three treatments, and will subsequently be followed up for 24 months. The primary analysis will be conducted using the 12-month data. The study is designed to evaluate the superiority of RG and NV over FH in terms of the rate of revision surgery for pedicle screw malposition. This study protocol was compiled according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement.[26] Thirteen European centers from the Netherlands, Switzerland, Germany, Austria, and France will participate in recruitment. Most centers will contribute to at least two of the three study arms.

Study Population

Inclusion Criteria

Patients with the following indications for thoracolumbar pedicle screw placement will be considered: Degenerative pathologies (spinal stenosis, spondylolisthesis, degenerative disc disease, recurrent disc herniation), infections, vertebral tumors, as well as traumatic and osteoporotic fractures. Patients are required to give informed consent. Only patients aged 18 or older will be considered for inclusion.

Exclusion Criteria

Patients undergoing deformity surgery for scoliosis or kyphosis will be excluded. Patients undergoing surgery at more than 5 vertebral levels will not be considered.

Patient and Public Involvement

Patients were not involved in the development of the research question or study design, and will not be involved in recruitment or conduct of the study.

Study Procedures

Participating surgeons will screen all patients with an indication for thoracolumbar pedicle screw placement for eligibility during the first consultation. If eligible, the patient will receive an informative letter containing details on the EUROSPIN study, including risks and benefits of participation. If written informed consent is given, the clinician or study nurse will record baseline data. At this first clinical visit, group allocation will be determined.

Group Allocation

This is a non-randomized study. In this study, we decided not to randomly allocate patients to treatment and control groups. Instead, patients will undergo pedicle screw placement with the technique that the treating surgeon is most experienced with, and for which equipment is available at the center. In this way, our study design closely approximates that of the "expertise-based trial" suggested by Devereaux et al.[23] One reason concerns the surgeons' level of experience with a particular technique.[16,20,27,28] Because it has been demonstrated that the learning curve for some instrumentation techniques is steep, we did not deem it rational to have surgeons carry out procedures with a technique that they are not experienced with.[29] Instead, surgeons will carry out the procedures with the technique that they are highly experienced with. This will allow us to compare true effectiveness, similar to a prospective registry, as opposed to efficacy.[25] We have not implemented a pre-study "learning curve" phase accordingly. A second reason is recruitment. Although some randomized controlled trials on robotic guidance in spinal instrumentation have been successful [16,30,31], they have suffered from rather slow recruitment and consequently relatively low power to demonstrate differences in an infrequently

occurring endpoint, such as our primary endpoint. Multiple initialized randomized studies even had to be closed prematurely due to slow recruitment.[22]

Blinding

This is an open-label study. Both patients and treating physicians will be aware of group allocation. However, the primary analysis will be carried out by an epidemiologist blinded to group allocation, according to the pre-specified statistical protocol. Rating of CT images will be carried out by independent radiologists blinded to group allocation.

Treatment Groups

Experimental Intervention I: Robot-guided pedicle screw placement

Robotic guidance in the form of the following systems will be applied: Mazor X, Renaissance, or SpineAssist (Mazor Robotics, Ltd., Ceasarea, Israel) or ROSA Spine (Zimmer Biomet, Warsaw, IN, USA).[5,14,16,18,19,21] Fluoroscopic control will be available.

Experimental Intervention II: Navigated pedicle screw placement

Navigated procedures will be carried out under image guidance connected to a computer-assisted navigation system.[4,5,15] Preoperative or intraoperative image acquisition by spiral CT, cone-beam CT (O-Arm), or three-dimensional isocentric flurosocopy (3DFL) will be applied for navigation.[4,5,15,32–34] Fluoroscopic control will be available.

Control Intervention: Freehand pedicle screw placement

Conventional freehand surgery was chosen as the comparator because it is currently the most widely used and accepted standard technique around the world.[2] Freehand procedures will be carried out according to surgeon preference, under fluoroscopic control.[5,9,15,16,18,19,21,32] Computer assistance will not be available.

Cointerventions

Analgesic medication will be available to the patients, if necessary. In addition, patients will be able to undergo any further desired cointerventions such as elastic corsets or rigid casts, physiotherapy, or others.

Prognostic Factors

At the baseline assessment, patient age, height, weight, BMI, history of back or leg pain in months, prior surgery at any of the index levels, as well as highest level of education (elementary/high school/higher education/(post-)doctoral) and type of work (employed/self-employed/housework/student/retired/unemployed) will be recorded. We will also assess the use of analgesic medication (daily/at least once a week/not regularly) including over-the-counter drugs, patient satisfaction with current symptoms on a 3-step Likert scale (satisfied/neutral/dissatisfied), smoking status (active smoker/ceased/never smoked), and working status (able to work/unable to work/not applicable).

Outcome Measures

Primary Endpoint

We defined the primary endpoint as time to revision surgery for a malpositioned or loosened pedicle screw within the first postoperative year. In patients who experienced the primary endpoint, CT imaging will be carried out before and after revision surgery, and the degree of malposition will be graded according to the classification described by Gertzbein and Robbins.[35]

Secondary Endpoints

A range of secondary endpoints will be assessed. The following patient-reported outcome measures (PROMs) will be captured at baseline and follow-up: Numeric Rating Scales (NRS) for back pain severity (NRS-BP) and leg pain severity (NRS-LP), as well as validated translations of version 2.1 of the Oswestry Disability Index (ODI) for subjective functional impairment, and the three-level version the EuroQOL 5-dimensions (EQ-5D-3L) questionnaire (EQ-5D index and thermometer) for health-related

quality of life (HRQOL).[36] The EQ-5D index will be evaluated according to the respective national tariffs.[37] The proportion of patients in which revision or redirection of a pedicle screw was required intraoperatively (intraoperative revision) will be recorded, as well as the number of instrumented index levels per patient. We will record whether the procedure was carried out in a minimally invasive or open approach, and capture duration of the procedure in minutes, total intraoperative radiation dose as dose area product (DAP) in mGy cm^2, estimated blood loss in mL, need for blood transfusion, as well as any intraoperative or postoperative adverse events. Conversions from one study arm to another, as well as from minimally invasive to open surgery will be tracked. All serious adverse events (SAEs) will be reported to the principal investigators' site.

Follow-Up

Patients will be followed up at 6 weeks, 12 months, and 24 months postoperatively (Table 1). At follow-up, PROMs, use of analgesic medication, satisfaction with symptoms, smoking status, time to return to work in weeks, as well as any reoperations will be captured.

Data Collection

Data will be collected using a validated, secure web-based electronic data capturing system (CASTOR EDC, Amsterdam, The Netherlands). Each center will be able to enter anonymized data into an Electronic Research Form (eCRF). Investigators from each center will assign identifiers to patients, and store demasking lists. For follow-up of patient-reported outcome measures (PROMs), centers will also have the option of dispatching standardized, scheduled surveys directly to the patients.[38] All data handling (data entry, storage, and analysis) is confidential and complies with data protection regulations of participating countries and the European Union. Anonymous data will be stored for 15 years.

Sample Size Calculation

It was determined that, to detect an intergroup difference of 5% in the primary endpoint, 205 patients are required per group to achieve a power of $1 - \beta = 0.8$ at $\alpha = 0.05$. The incidence rates were based on the published literature, with an approximated incidence rate of the primary endpoint of approximately 0% for the intervention and 5% for the control group.[5,14] Because the study protocol is in line with the normal clinical follow-up protocol of most centers, a low dropout rate is expected. This led to a minimum total sample size of 615 patients.

Statistical Analysis

Overview

All analyses will be carried out in R (The R Foundation for Statistical Computing).[39] A $p \leq 0.05$ on two-tailed tests will be considered statistically significant. The primary analysis, conducted on the 12-month data, will be carried out according to the intention-to-treat principle.[40] Results will be reported as effect size estimates and their 95% confidence intervals.

Analysis of Primary Endpoint

The effect on the primary endpoint will be reported as hazard ratios and their 95% confidence intervals, calculated from crude and adjusted Cox proportional hazards models. The primary endpoint will be specified as the dependent variable, and group assignment as the independent variable, with the FH group as the reference category. Patients who did not experience a primary endpoint will be censored at the 12-month follow-up.

Analysis of Secondary Endpoints

PROMs (NRS-BP, NRS-LP, ODI, EQ-5D) will be analysed using baseline-adjusted linear mixed models. The mean overall effect over time, as well as effects at the specific follow-up timepoints, will be

estimated. The proportions of patients achieving MCID for each PROM, as well as proportions of patients reporting satisfaction, return to work, reoperations, and using analgesic medication will be reported. Return to work and overall reoperations will be statistically analysed using crude and adjusted Cox proportional hazards models. In addition, intergroup comparison will be performed for patient satisfaction and use of analgesic medication by logistic regression.

Subgroup Analysis

Prespecified subgroup analyses of the primary outcome will be performed in the intention to-treat population to test for an interaction between study group and the subgroup variable. Stratified analyses will be performed by indication for surgery, specific device used, type of exposure, as well as single-level or multi-level fusion.

Monitoring

Monitoring will be performed according to the pre-specified monitor plan. An epidemiologist from the sponsor institution will organize an initiation monitor visit at every participating center before starting recruitment. This monitor visit will check whether all study staff are properly trained and the delegation of tasks are well documented (complete Investigator Site File, training and delegation logs). An additional audit will be carried out at 6 months after initiation of recruitment to check whether source documentation and eCRF documentation is similar. Throughout the entire study additional queries by the monitor are send to the investigator in the data capturing system to ensure proper data capturing.

Expected Completion

Recruitment is expected to be completed by January 2021, with the 2-year follow-up period extending to January 2023 for the final results.

Ethics and Dissemination

Ethical Approval and Study Registration

The study protocol is approved by the appropriate national and local authorities. Written informed consent will be obtained from all participants. This study is registered at ClinicalTrials.gov under the identifier NCT03398915.

Dissemination

The final results will be published in an international peer-reviewed scientific journal, and communicated to study participants. To avoid any bias, the results of any interim analyses will neither be shared with the investigators nor published until recruitment has been completed.

There are no further restrictions to publication.

Discussion

The EUROSPIN study is a large, multicentre, pragmatic study that is aimed at resolving the discussion on whether computer assistance in thoracolumbar instrumentation leads to measurable and clinically relevant improvements in patient-reported clinical outcome or complication rate.

Previous studies have created some evidence that both robotic guidance and navigation lead to a somewhat higher radiological accuracy than freehand pedicle screw insertion, with inconsistent results at a rather low level of evidence [7–13,15,16]. It is still unclear whether this increased radiological accuracy, usually measured as the degree of deviation from the desired transpedicular trajectory, translates to a clinical benefit to patients. It is hypothesized that, when using computer assistance, the lower rate of pedicular cortical encroachment leads to a lower incidence of radiculopathy [17,41], thus preventing revision surgery [14], decreasing overall treatment costs [42], and improving overall patient-oriented outcomes.[30] A meta-analysis has demonstrated that both robotic guidance and navigation lower the incidence of revision surgery for malpositioned pedicle screws.[5] However, the rate of intraoperative

screw revisions was markedly but not statistically significantly increased, the quality of the included individual studies was low, and it was determined that prospective studies assessing this research question with larger sample sizes are necessary to draw conclusions.[5] In addition, there are only very few, small studies comparing robotic guidance to navigation directly.[22,43] For these reasons, we designed our study to address these biases, and to provide higher-level evidence on clinical questions, comparing all three concepts of pedicle screw placement.

A specific goal of the EUROSPIN trial was to avoid potential conflicts of interest. Therefore, we declined any sort of involvement and financial support by the industry, and aimed to minimize personal conflict of interests with device manufacturers. This will enable unbiased execution and critical appraisal of the study results.[44]

The study has some limitations. First, for logistical and practical reasons, not all studies will be able to contribute to all three study arms. This may create center bias. However, the rationale for this design was to prospectively collect data obtained from surgeons highly experienced with the three techniques, resulting in a design similar to a prospective multicentre registry. Furthermore, we are unable to conduct a detailed evaluation of cost-effectiveness. The cost-value relationship of robotic and intraoperative imaging systems remains controversial, and it is as of yet unclear if there are any demonstrable clinical benefits that warrant the high acquisition and maintenance costs inherent to these systems.

Lastly, patients will not be randomly assigned to treatment groups in this study. As detailed above, there are two main reasons that randomization was deemed disadvantageous in this specific study. First, most centers do not have both a robotic system and conventional neuronavigation available, making it impossible to randomize to all three groups at every center. Furthermore, we aim to have the surgeons perform the procedures with the technique they are most experienced with.[20,28] This enables us to compare the treatment modalities in a more clinically applicable scenario, assessing effectiveness instead

of study-specific efficacy, similar to a prospective registry.[25] This corresponds to the idea of an "expertise-based trial".[23] Accordingly, no "learning curve" phase was implemented. In addition, some commenced randomized trials comparing robotic surgery with conventional techniques have had to be declared futile due to slow recruitment, usually because of a patient preference towards newer techniques. A split design, similar to the Spine Patient Outcomes Research Trial (SPORT), with a randomized and non-randomized subgroup was available as an alternative.[45] However, due to the aforementioned logistic difficulties and possible bias in experience, we have decided upon a simple, registry-like study design.

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Tables

Table 1 Chart demonstrating items collected at baseline and follow-up.

Item	Baseline	Surgery	Discharge	6 weeks postop.	12 months postop.	24 months postop.
Informed consent	X					
Group allocation	X					
Demographics	X					
Surgery		X				
Intraoperative parameters		X				
Perioperative parameters		X	X			
Blood transfusion		X	X			
Length of stay			X			
ODI	X			X	X	X
NRS-BP + NRS-LP	X			X	X	X
EQ-5D-3L	X			X	X	X
Satisfaction (Likert)	X			X	X	X
Work status	X			X	X	X
Smoking status	X			X	X	X
Use of analgesia	X			X	X	X
Intraoperative screw revision		X				
Revision surgery for screw malposition or loosening	With occurrence					
Computed tomography	With occurrence of revision surgery					
Adverse events	With occurrence					
Reoperations	With occurrence					
Other treatments	With occurrence					

EQ-5D-3L, 3-level version of the EuroQOL five-dimensions questionnaire; NRS-BP, numeric rating scale for back pain severity; NRS-LP, numeric rating scale for leg pain severity; ODI, Oswestry Disability Index;

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract
	2b	All items from the World Health Organization Trial Registration Data Set	WHO Supplement (only for editors)
Protocol version	3	Date and version identifier	WHO Supplement (only for editors)
Funding	4	Sources and types of financial, material, and other support	3-4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3
	5b	Name and contact information for the trial sponsor	4
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3-4
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8, Registration
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10,11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11,12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12,13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12,13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12,15

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	3,4
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A, WHO supplement
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not provided
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The European Robotic Spinal Instrumentation (EUROSPIN) study: Protocol for a multicenter prospective observational study of pedicle screw revision surgery after robot-guided, navigated, and freehand thoracolumbar spinal fusion

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The European Robotic Spinal Instrumentation (EUROSPIN) study: Protocol for a multicenter prospective observational study of pedicle screw revision surgery after robot-guided, navigated, and freehand thoracolumbar spinal fusion

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This study protocol has never previously been submitted for review in any medium, and has not been presented at any conferences.

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Competing Interests

JFCW reports consultancies for Safe Orthopaedics, Zimmer-Biomet, Silony, and EIT. FH reports a consultancy for Evospine. ML reports a consultancy for Zimmer-Biomet Robotics. YMR reports a consultancy for Icotec, and has received honoraria from Brainlab, DePuy Synthes, Medtronic, Spineart, Ulrich Medical, and Zeiss Medical. SMK reports consultancies for Nexstim, Brainlab, and Spineart Deutschland, and has received honoraria from Medtronic and Carl Zeiss Meditec. BM reports consultancies for Medtronic, Brainlab, and DePuy Synthes. PPG reports a consultancy for DePuy Synthes. CT reports receiving research supports and honoraria from DePuy Synthes, Icotec, Medtronic Intrinsic Therapeutics, Signus Medical, Brainlab, and Pfizer. ET reports consultancies for DePuy Synthes, Spineart, Medtronic, and Brainlab. All other authors declare that the protocol and its content were composed in the absence of any commercial or financial relationships that could be construed as a potential competing interest.

Author Contributions

VES, GM, PMvK, ET, MLS conceived and designed the study. VES, PMvK, JWRT conceived the statistical analysis plan. VES, GM, PMvK, ET, MLS prepared the first draft of the study protocol. VES, GM, PMvK, HAJE, AA, CB, JFCW, SU, FH, CGS, MAS, ML, JP, DB, IF, BS, VR, YMR, SMK, BM, NK, PPG, CT, JWRT, ET, MLS contributed to the final design of this study protocol, assisted with drafting the manuscript, and carried out a critical revision of the manuscript. VES, GM, PMvK, HAJE, AA, CB, JFCW, SU, FH, CGS, MAS, ML, JP, DB, IF, BS, VR, YMR, SMK, BM, NK, PPG, CT, JWRT,

ET, MLS approved the final version of the manuscript and agree to be accountable for the accuracy of the work. MLS supervised the work and is the guarantor.

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Abstract

Introduction

Robotic guidance (RG) and computer-assisted navigation (NV) have seen increased adoption in instrumented spine surgery over the past decade. Although there exists some evidence that these techniques increase radiological pedicle screw accuracy compared to conventional freehand (FH) surgery, this may not directly translate to any tangible clinical benefits, especially considering the relatively high inherent costs. As a non-randomized, expertise-based study, the European Robotic Spinal Instrumentation (EUROSPIN) Study aims to create prospective multicenter evidence on the potential comparative clinical benefits of RG, NV, and FH in a real-world setting.

Methods and Analysis

Patients will be allocated in a non-randomized, non-blinded fashion to the RG, NV, or FH arms. Adult patients that are to undergo thoracolumbar pedicle screw instrumentation for degenerative pathologies, infections, vertebral tumors, or fractures will be considered for inclusion. Deformity correction and surgery at more than 5 levels represent exclusion criteria. Follow-up will take place at 6 weeks, as well as 12 and 24 months. The primary endpoint was defined as the time to revision surgery for a malpositioned or loosened pedicle screw within the first postoperative year. Secondary endpoints include patient-reported back and leg pain, as well as Oswestry Disability Index and EQ-5D questionnaires. Use of analgesic medication and work status will be recorded. The primary analysis, conducted on the 12-month data, will be carried out according to the intention-to-treat principle. The primary endpoint will be analysed using crude and adjusted Cox proportional hazards models. Patient-reported outcomes will be analysed using baseline-adjusted linear mixed models. The study will be monitored according to a pre-specified monitoring plan.

Ethics and Dissemination

The study protocol is approved by the appropriate national and local authorities. Written informed consent will be obtained from participants. The final results will be published in an international peer-reviewed journal.

Trial Registration Number

NCT03398915; Pre-results, recruiting stage

Strengths and Limitations of this Study

- Large, pragmatic, prospective observational controlled study carried out in thirteen pan-European centers
- Long-term, 2-year follow-up with standardised and validated patient-reported outcomes
- Non-randomized "expertise-based" study design
- Even with adjusted analyses, lack of randomization may introduce biases
- Potential performance bias due to lack of blinding of surgeons and patients

Introduction

In the Unites States alone, an estimated 3.6 million spinal instrumentations were performed between 2001 and 2010, with an associated $287 billion in total healthcare charges.[1] Both numbers demonstrate a steadily increasing trend.[1] In 2013, only 11% of spine surgeons routinely used navigation systems.[2] Meanwhile, more and more surgeons are implementing computer assistance into their clinical practice, one reason being the adoption of minimally invasive (MI) techniques, further increasing the need for navigation due to often inexistent line-of-sight.[2,3]

In 1995, the concept of computer-assisted navigation was introduced to spine surgery.[4] Modern navigation systems (NV) assist in pedicle screw insertion by projecting screw trajectories onto pre- or intraoperatively obtained and co-registered computed tomography (CT) or 3D-fluoroscopic (3DFL) images.[5] Robotic guidance (RG), introduced in 2006, takes one further step by providing mechanical guidance according to pre-planned screw trajectories, eliminating the need of on-the-spot establishment of trajectories by the surgeon.[6–8] These systems can be considered cooperative robots ("cobots"), since they do not insert screws autonomously, rather exclusively providing stable guidance.[9] To achieve mechanical guidance, the robot's working channel moves into the pre-planned trajectory based on co-registration of preoperative and intraoperative imaging while accounting for any potential differences in real-time spinal anatomy such as those caused by distraction, cage insertion, or changes between the supine positioning on preoperative CT and prone positioning during surgery.[6–8,10,11] By restricting the surgeon's natural full motion range of 6 degrees of freedom (DOF) to 2 DOFs – motion up and down as well as yaw in the cannula – the robot guides the surgeon's tool according to the pre-defined trajectories while simultaneously providing stability for drilling, which is assumed to result in greater radiological screw accuracy.[6] When comparing the published literature on FG, NV, and RG, rates of radiologically well-placed screws of 69%-94% for FH, 81%-100% for NV, and 85% to 98% for RG are found[6,10–15], with significant differences among subgroups of various NV devices.[16]

While there is some evidence that RG and NV lead to higher radiological accuracy than freehand (FH) instrumentation [12,16–21], this may not translate directly to real-world clinical benefits, especially in light of the high acquisition and maintenance costs inherent to these systems.[22] A recent systematic review on the cost-effectiveness of RG concluded that, although the technology is often claimed to be cost-effective, there appears to be a lack of published data to warrant this statement.[22] Possible benefits could include shorter operating times, and decreased incidences of radiculopathy and costly revision surgery for screw malposition, although the current level of evidence is very low, and there are no large prospective controlled studies comparing clinically relevant outcome such as pedicle screw-related revision surgery, as opposed to radiological surrogate measures alone.[5,6,14,21–30]

Currently, few published studies compare these techniques in a prospective setting, although they often suffer from insufficient power to demonstrate any potential clinical benefits, or report major conflicts of interests. Furthermore, while many studies compare RG to FH, there are no powerful studies comparing RG and NV.[5] We aim to conduct a prospective observational controlled study comparing RG, NV, and FH to create unbiased real-world evidence on these instrumentation techniques.[31]

Methods and Analysis

Study Design

The European Robotic Spinal Instrumentation (EUROSPIN) study is a prospective, international, multicentre, pragmatic, open-label, non-randomized, observational controlled study comparing the effectiveness of three techniques for pedicle screw instrumentation, namely RG, NV (CT-, O-Arm, or 3DFL-based), and FH.[31–33] Following the baseline evaluation, patients will receive one of the three treatments, and will subsequently be followed up for 24 months. The primary analysis will be conducted using the 12-month data. The study is designed to evaluate the superiority of RG and NV over FH in terms of the rate of revision surgery for pedicle screw malposition. This study protocol was compiled according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement.[34] Thirteen European centers from the Netherlands, Switzerland, Germany, Austria, and France will participate in recruitment. Most centers will contribute to at least two of the three study arms.

Study Population

Inclusion Criteria

Patients with the following indications for thoracolumbar pedicle screw placement will be considered: Degenerative pathologies (spinal stenosis, spondylolisthesis, degenerative disc disease, recurrent disc herniation), infections, vertebral tumors, as well as traumatic and osteoporotic fractures. Patients are required to give informed consent. Only patients aged 18 or older will be considered for inclusion.

Exclusion Criteria

Patients undergoing deformity surgery for scoliosis or kyphosis will be excluded. Patients undergoing surgery at more than 5 vertebral levels will not be considered.

Patient and Public Involvement

Patients were not involved in the development of the research question or study design, and will not be involved in recruitment or conduct of the study.

Study Procedures

Participating surgeons will screen all patients with an indication for thoracolumbar pedicle screw placement for eligibility during the first consultation. If eligible, the patient will receive an informative letter containing details on the EUROSPIN study after surgical consent has been given, including risks and benefits of participation. If written informed consent for study participation is given, the clinician or study nurse will record baseline data. At this first visit, group allocation will be determined.

Group Allocation

This is a non-randomized study. In this study, we decided not to randomly allocate patients to treatment and control groups. Instead, patients will undergo pedicle screw placement with the technique that the treating surgeon is most experienced with, and for which equipment is available at the center.[31] One reason concerns the surgeons' level of experience with a particular technique.[14,27,35,36] Because it has been demonstrated that the learning curve for some instrumentation techniques is steep, we did not deem it rational to have surgeons carry out procedures with a technique that they are not experienced with.[37] Instead, surgeons will carry out the procedures with the technique that they are highly experienced with. This will allow us to compare true effectiveness, similar to a prospective registry, as opposed to efficacy.[33] We have not implemented a pre-study "learning curve" phase accordingly. A second reason is recruitment. Although some randomized controlled trials on robotic guidance in spinal instrumentation have been successful [14,38,39], they have suffered from rather slow recruitment and consequently relatively low power to demonstrate differences in an infrequently occurring endpoint, such as our primary endpoint. Multiple initialized randomized studies even had to be closed prematurely due to slow recruitment.[29]

Blinding

This is an open-label study. Both patients and treating physicians will be aware of group allocation. However, the primary analysis will be carried out by an epidemiologist blinded to group allocation, according to the pre-specified statistical protocol. Rating of CT images will be carried out by independent radiologists blinded to group allocation.

Treatment Groups

Experimental Intervention I: Robot-guided pedicle screw placement

Robotic guidance in the form of the following systems will be applied: Mazor X, Renaissance, or SpineAssist (Mazor Robotics, Ltd., Ceasarea, Israel) or ROSA Spine (Zimmer Biomet, Warsaw, IN, USA).[5,6,14,25,26,28] Fluoroscopic control will be available.

Experimental Intervention II: Navigated pedicle screw placement

Navigated procedures will be carried out under image guidance connected to a computer-assisted navigation system.[4,5,23] Preoperative or intraoperative image acquisition by spiral CT, cone-beam CT (O-Arm), or three-dimensional isocentric flurosocopy (3DFL) will be applied for navigation.[4,5,23,40–42] Fluoroscopic control will be available.

Control Intervention: Freehand pedicle screw placement

Conventional freehand surgery was chosen as the comparator because it is currently the most widely used and accepted standard technique around the world.[2] Freehand procedures will be carried out according to surgeon preference, under fluoroscopic control.[5,14,19,23,25,26,28,40] Computer assistance will not be available.

Cointerventions

Analgesic medication will be available to the patients, if necessary. In addition, patients will be able to undergo any further desired cointerventions such as elastic corsets or rigid casts, physiotherapy, or others.

Prognostic Factors

At the baseline assessment, patient age, height, weight, BMI, history of back or leg pain in months, prior surgery at any of the index levels, as well as highest level of education (elementary/high school/higher education/(post-)doctoral) and type of work (employed/self-employed/housework/student/retired/unemployed) will be recorded. We will also assess the use of analgesic medication (daily/at least once a week/not regularly) including over-the-counter drugs, patient satisfaction with current symptoms on a 3-step Likert scale (satisfied/neutral/dissatisfied), smoking status (active smoker/ceased/never smoked), and working status (able to work/unable to work/not applicable). Documented osteoporosis with or without treatment will be recorded, as well as any procedures for osteoporotic fractures.

Outcome Measures

Primary Endpoint

We defined the primary endpoint as time to revision surgery for a malpositioned or loosened pedicle screw within the first postoperative year. In patients who experienced the primary endpoint, CT imaging will be carried out before revision surgery, and the degree of malposition will be graded according to the classification described by Gertzbein and Robbins.[43]

Secondary Endpoints

A range of secondary endpoints will be assessed. The following patient-reported outcome measures (PROMs) will be captured at baseline and follow-up: Numeric Rating Scales (NRS) for back pain severity (NRS-BP) and leg pain severity (NRS-LP), as well as validated translations of version 2.1 of the

Oswestry Disability Index (ODI) for subjective functional impairment, and the three-level version the EuroQOL 5-dimensions (EQ-5D-3L) questionnaire (EQ-5D index and thermometer) for health-related quality of life (HRQOL).[44] The EQ-5D index will be evaluated according to the respective national tariffs.[45] The proportion of patients in which revision or redirection of a pedicle screw was required intraoperatively (intraoperative revision) will be recorded, as well as the number of instrumented index levels per patient. We will record whether the procedure was carried out in a minimally invasive or open approach, and capture duration of the procedure in minutes, total intraoperative fluoroscopic radiation dose as dose area product (DAP) in mGy × cm^2, estimated blood loss in mL, need for blood transfusion, as well as any intraoperative or postoperative adverse events. We will also record the level of experience of the surgeon placing the pedicle screws. Conversions from one study arm to another, as well as from minimally invasive to open surgery will be tracked. All serious adverse events (SAEs) will be reported to the principal investigators' site.

Follow-Up

Patients will undergo an "early" follow-up at one to three months. Subsequently, patients will be followed-up at 12 months and 24 months postoperatively (Table 1). At follow-up, PROMs, use of analgesic medication, satisfaction with symptoms, smoking status, time to return to work in weeks, as well as any reoperations will be captured.

Data Collection

Data will be collected using a validated, secure web-based electronic data capturing system (CASTOR EDC, Amsterdam, The Netherlands). Each center will be able to enter anonymized data into an Electronic Research Form (eCRF). Investigators from each center will assign identifiers to patients, and store demasking lists. For follow-up of patient-reported outcome measures (PROMs), centers will also have the option of dispatching standardized, scheduled surveys directly to the patients.[46] All data handling (data

entry, storage, and analysis) is confidential and complies with data protection regulations of participating countries and the European Union. Anonymous data will be stored for 15 years.

Sample Size Calculation

It was determined that, to detect an intergroup difference of 5% in the primary endpoint, 205 patients are required per group to achieve a power of $1 - \beta = 0.8$ at $\alpha = 0.05$.[47] Recruitment for a specific arm will be stopped once the 205 patients have been included. The incidence rates were based on the published literature, with an approximated incidence rate of the primary endpoint of approximately 0% for the intervention and 5% for the control group.[5,6] Because the study protocol is in line with the normal clinical follow-up protocol of most centers, a low dropout rate is expected. This led to a minimum total sample size of 615 patients.

Statistical Analysis

Overview

All analyses will be carried out in R (The R Foundation for Statistical Computing).[48] A $p \leq 0.05$ on two-tailed tests will be considered statistically significant. The primary analysis, conducted on the 12-month data, will be carried out according to the intention-to-treat principle, with the intention-to-treat definition applying to the index surgery.[49] Results will be reported as effect size estimates and their 95% confidence intervals.

Analysis of Primary Endpoint

The effect on the primary endpoint will be reported as hazard ratios and their 95% confidence intervals, calculated from crude and adjusted Cox proportional hazards models. The crude model will be considered the primary analysis. The primary endpoint will be specified as the dependent variable, and group assignment as the independent variable, with the FH group as the reference category. Our null hypothesis

is that neither RG nor NV lead to a significant decrease in the primary endpoint incidence compared to FH. Patients who did not experience a primary endpoint will be censored at the 12-month follow-up.

Analysis of Secondary Endpoints

PROMs (NRS-BP, NRS-LP, ODI, EQ-5D) will be analysed using baseline-adjusted linear mixed models. The mean overall effect over time, as well as effects at the specific follow-up timepoints, will be estimated. The proportions of patients achieving MCID for each PROM, as well as proportions of patients reporting satisfaction, return to work, reoperations, and using analgesic medication will be reported. MCIDs for the ODI, NRS-BP, and NRS-LP were defined as a reduction of ≥ 30% according to Ostelo et al.[50] The MCID threshold for the EQ-5D was set to 0.2 points according to Asher et al.[51] Return to work and overall reoperations will be statistically analysed using crude and adjusted Cox proportional hazards models. In addition, intergroup comparison will be performed for patient satisfaction and use of analgesic medication by logistic regression.

Subgroup Analysis

Prespecified subgroup analyses of the primary outcome will be performed in the intention to-treat population to test for an interaction between study group and the subgroup variable. Stratified analyses will be performed by indication for surgery, specific device used, type of exposure, as well as single-level or multi-level fusion.

Monitoring

Monitoring will be performed according to the pre-specified monitor plan. An epidemiologist from the sponsor institution will organize an initiation monitor visit at every participating center before starting recruitment. This monitor visit will check whether all study staff are properly trained and the delegation of tasks are well documented (complete Investigator Site File, training and delegation logs). An additional audit will be carried out at 6 months after initiation of recruitment to check whether source documentation

and eCRF documentation is similar. Throughout the entire study additional queries by the monitor are send to the investigator in the data capturing system to ensure proper data capturing.

Expected Completion

Recruitment is expected to be completed by January 2021, with the 2-year follow-up period extending to January 2023 for the final results.

Ethics and Dissemination

Ethical Approval and Study Registration

The study protocol is approved by the appropriate national and local authorities. Written informed consent will be obtained from all participants. This study is registered at ClinicalTrials.gov under the identifier NCT03398915.

Dissemination

The final results will be published in an international peer-reviewed scientific journal, and communicated to study participants. To avoid any bias, the results of any interim analyses will neither be shared with the investigators nor published until recruitment has been completed.

There are no further restrictions to publication.

Discussion

The EUROSPIN study is a large, multicentre, pragmatic study that is aimed at resolving the discussion on whether computer assistance in thoracolumbar instrumentation leads to measurable and clinically relevant improvements in patient-reported clinical outcome or complication rate.

Previous studies have created some evidence that both robotic guidance and navigation lead to a somewhat higher radiological accuracy than freehand pedicle screw insertion, with inconsistent results at a rather low level of evidence [12,14,16–21,23]. It is still unclear whether this increased radiological accuracy, usually measured as the degree of deviation from the desired transpedicular trajectory, translates to a clinical benefit to patients. It is hypothesized that, when using computer assistance, the lower rate of pedicular cortical encroachment leads to a lower incidence of radiculopathy [24,52], thus preventing revision surgery [6], decreasing overall treatment costs [53], and improving overall patient-oriented outcomes.[38] A meta-analysis has demonstrated that both robotic guidance and navigation lower the incidence of revision surgery for malpositioned pedicle screws.[5] However, the rate of intraoperative screw revisions was markedly but not statistically significantly increased, the quality of the included individual studies was low, and it was determined that prospective studies assessing this research question with larger sample sizes are necessary to draw conclusions.[5] In addition, there are only very few, small studies comparing robotic guidance to navigation directly.[29,54] For these reasons, we designed our study to address these biases, and to provide higher-level evidence on clinical questions, comparing all three concepts of pedicle screw placement.

A specific goal of the EUROSPIN trial was to avoid potential conflicts of interest. Therefore, we declined any sort of involvement and financial support by the industry, and aimed to minimize personal conflict of interests with device manufacturers. This will enable unbiased execution and critical appraisal of the study results.[55]

The study has some limitations. First, for logistical and practical reasons, not all sites will be able to contribute to all three study arms. This may create center bias. However, the rationale for this design was to prospectively collect data obtained from surgeons experienced with the three techniques, resulting in a design similar to a prospective multicentre registry. Furthermore, we are unable to conduct a detailed evaluation of cost-effectiveness. The cost-value relationship of robotic and intraoperative imaging systems remains controversial, and it is as of yet unclear if there are any demonstrable clinical benefits that warrant the high acquisition and maintenance costs inherent to these systems.[22] In addition, preoperative radiation that may be required for surgical planning may differ among the groups, and is not captured. In this light, it is important to consider that, even if the navigated and robotic techniques would result in decreased intraoperative radiation, this benefit to the patient may be levelled out by the additional radiation dose necessary for planning.

Furthermore, although all participating surgeons were experienced with the respective techniques applied, as we did not specify a minimum case number for participating surgeons, surgeon experience may constitute a potential bias. We aim to correct for this potential bias by collecting data on the degree of experience of the surgeons placing the pedicle screws, which allows for statistical adjustment if necessary. Another potential limitation exists in the fact that thresholds for revision of a malpositioned or loosened screw may vary among centers and surgeons. Moreover, our study is likely underpowered for subgroup analyses analysing treatment effects among the single devices and the different indications for surgery. Lastly, some potential confounders such as comorbidities and symptom duration are not collected.

Patients will not be randomly assigned to treatment groups in this study. As detailed above, there are two main reasons that randomization was deemed disadvantageous in this specific study. First, most centers do not have both a robotic system and conventional neuronavigation available, making it impossible to randomize to all three groups at every center. Furthermore, we aim to have the surgeons perform the

procedures with the technique they are most experienced with.[27,31,36] This enables us to compare the treatment modalities in a more clinically applicable scenario, assessing effectiveness instead of study-specific efficacy, similar to a prospective registry.[33] Accordingly, no "learning curve" phase was implemented. Even for randomized studies, Devereaux et al. suggest that surgeon-based or "expertise-based" group assignment, in which patients are not randomized to treatments but rather to clinicians experienced with a certain treatment, may lead to greater real-world applicability of study results.[31] In addition, some commenced randomized trials comparing robotic surgery with conventional techniques have had to be declared futile due to slow recruitment, usually because of a patient preference towards newer techniques. A split design, similar to the Spine Patient Outcomes Research Trial (SPORT), with a randomized and non-randomized subgroup was available as an alternative.[56] However, due to the aforementioned logistic difficulties and possible bias in experience, we have decided upon a simple, registry-like study design.

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Tables

Table 1 Chart demonstrating items collected at baseline and follow-up.

Item	Baseline	Surgery	Discharge	1 to 3 months postop.	12 months postop.	24 months postop.
Informed consent	X					
Group allocation	X					
Demographics	X					
Surgeon experience		X				
Surgery		X				
Intraoperative parameters		X				
Perioperative parameters		X	X			
Blood transfusion		X	X			
Length of stay			X			
ODI	X			X	X	X
NRS-BP + NRS-LP	X			X	X	X
EQ-5D-3L	X			X	X	X
Satisfaction (Likert)	X			X	X	X
Work status	X			X	X	X
Smoking status	X			X	X	X
Use of analgesia	X			X	X	X
Intraoperative screw revision		X				
Revision surgery for screw malposition or loosening	With occurrence					
Computed tomography	With occurrence of revision surgery					
Adverse events	With occurrence					
Reoperations	With occurrence					
Other treatments	With occurrence					

EQ-5D-3L, 3-level version of the EuroQOL five-dimensions questionnaire; NRS-BP, numeric rating scale for back pain severity; NRS-LP, numeric rating scale for leg pain severity; ODI, Oswestry Disability Index;

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract
	2b	All items from the World Health Organization Trial Registration Data Set	WHO Supplement (only for editors)
Protocol version	3	Date and version identifier	WHO Supplement (only for editors)
Funding	4	Sources and types of financial, material, and other support	3-4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3
	5b	Name and contact information for the trial sponsor	4
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3-4
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8, Registration
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10,11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11,12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12,13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12,13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12,15

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	3,4
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A, WHO supplement
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not provided
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The European Robotic Spinal Instrumentation (EUROSPIN) study: Protocol for a multicenter prospective observational study of pedicle screw revision surgery after robot-guided, navigated, and freehand thoracolumbar spinal fusion

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The European Robotic Spinal Instrumentation (EUROSPIN) study: Protocol for a multicenter prospective observational study of pedicle screw revision surgery after robot-guided, navigated, and freehand thoracolumbar spinal fusion

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This study protocol has never previously been submitted for review in any medium, and has not been presented at any conferences.

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Protocol for the EUROSPIN Study

Competing Interests

JFCW reports consultancies for Safe Orthopaedics, Zimmer-Biomet, Silony, and EIT. FH reports a consultancy for Evospine. ML reports a consultancy for Zimmer-Biomet Robotics. YMR reports a consultancy for Icotec, and has received honoraria from Brainlab, DePuy Synthes, Medtronic, Spineart, Ulrich Medical, and Zeiss Medical. SMK reports consultancies for Nexstim, Brainlab, and Spineart Deutschland, and has received honoraria from Medtronic and Carl Zeiss Meditec. BM reports consultancies for Medtronic, Brainlab, and DePuy Synthes. PPG reports a consultancy for DePuy Synthes. CT reports receiving research supports and honoraria from DePuy Synthes, Icotec, Medtronic Intrinsic Therapeutics, Signus Medical, Brainlab, and Pfizer. ET reports consultancies for DePuy Synthes, Spineart, Medtronic, and Brainlab. All other authors declare that the protocol and its content were composed in the absence of any commercial or financial relationships that could be construed as a potential competing interest.

Author Contributions

VES, GM, PMvK, ET, MLS conceived and designed the study. VES, PMvK, JWRT conceived the statistical analysis plan. VES, GM, PMvK, ET, MLS prepared the first draft of the study protocol. VES, GM, PMvK, HAJE, AA, CB, JFCW, SU, FH, CGS, MAS, ML, JP, DB, IF, BS, VR, YMR, SMK, BM, NK, PPG, CT, JWRT, ET, MLS contributed to the final design of this study protocol, assisted with drafting the manuscript, and carried out a critical revision of the manuscript. VES, GM, PMvK, HAJE, AA, CB, JFCW, SU, FH, CGS, MAS, ML, JP, DB, IF, BS, VR, YMR, SMK, BM, NK, PPG, CT, JWRT,

ET, MLS approved the final version of the manuscript and agree to be accountable for the accuracy of the work. MLS supervised the work and is the guarantor.

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Study Sponsor and Principal Investigator

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Abstract

Introduction

Robotic guidance (RG) and computer-assisted navigation (NV) have seen increased adoption in instrumented spine surgery over the past decade. Although there exists some evidence that these techniques increase radiological pedicle screw accuracy compared to conventional freehand (FH) surgery, this may not directly translate to any tangible clinical benefits, especially considering the relatively high inherent costs. As a non-randomized, expertise-based study, the European Robotic Spinal Instrumentation (EUROSPIN) Study aims to create prospective multicenter evidence on the potential comparative clinical benefits of RG, NV, and FH in a real-world setting.

Methods and Analysis

Patients are allocated in a non-randomized, non-blinded fashion to the RG, NV, or FH arms. Adult patients that are to undergo thoracolumbar pedicle screw instrumentation for degenerative pathologies, infections, vertebral tumors, or fractures are considered for inclusion. Deformity correction and surgery at more than 5 levels represent exclusion criteria. Follow-up takes place at 6 weeks, as well as 12 and 24 months. The primary endpoint is defined as the time to revision surgery for a malpositioned or loosened pedicle screw within the first postoperative year. Secondary endpoints include patient-reported back and leg pain, as well as Oswestry Disability Index and EQ-5D questionnaires. Use of analgesic medication and work status are recorded. The primary analysis, conducted on the 12-month data, is carried out according to the intention-to-treat principle. The primary endpoint is analysed using crude and adjusted Cox proportional hazards models. Patient-reported outcomes are analysed using baseline-adjusted linear mixed models. The study is monitored according to a pre-specified monitoring plan.

Ethics and Dissemination

The study protocol is approved by the appropriate national and local authorities. Written informed consent is obtained from all participants. The final results will be published in an international peer-reviewed journal.

Trial Registration Number

NCT03398915; Pre-results, recruiting stage

Strengths and Limitations of this Study

- Large, pragmatic, prospective observational controlled study carried out in thirteen pan-European centers
- Long-term, 2-year follow-up with standardised and validated patient-reported outcomes
- Non-randomized "expertise-based" study design
- Even with adjusted analyses, lack of randomization may introduce biases
- Potential performance bias due to lack of blinding of surgeons and patients

Introduction

In the Unites States alone, an estimated 3.6 million spinal instrumentations were performed between 2001 and 2010, with an associated $287 billion in total healthcare charges.[1] Both numbers demonstrate a steadily increasing trend.[1] In 2013, only 11% of spine surgeons routinely used navigation systems.[2] Meanwhile, more and more surgeons are implementing computer assistance into their clinical practice, one reason being the adoption of minimally invasive (MI) techniques, further increasing the need for navigation due to often inexistent line-of-sight.[2,3]

In 1995, the concept of computer-assisted navigation was introduced to spine surgery.[4] Modern navigation systems (NV) assist in pedicle screw insertion by projecting screw trajectories onto pre- or intraoperatively obtained and co-registered computed tomography (CT) or 3D-fluoroscopic (3DFL) images.[5] Robotic guidance (RG), introduced in 2006, takes one further step by providing mechanical guidance according to pre-planned screw trajectories, eliminating the need of on-the-spot establishment of trajectories by the surgeon.[6–8] These systems can be considered cooperative robots ("cobots"), since they do not insert screws autonomously, rather exclusively providing stable guidance.[9] To achieve mechanical guidance, the robot's working channel moves into the pre-planned trajectory based on co-registration of preoperative and intraoperative imaging while accounting for any potential differences in real-time spinal anatomy such as those caused by distraction, cage insertion, or changes between the supine positioning on preoperative CT and prone positioning during surgery.[6–8,10,11] By restricting the surgeon's natural full motion range of 6 degrees of freedom (DOF) to 2 DOFs – motion up and down as well as yaw in the cannula – the robot guides the surgeon's tool according to the pre-defined trajectories while simultaneously providing stability for drilling, which is assumed to result in greater radiological screw accuracy.[6] When comparing the published literature on FG, NV, and RG, rates of radiologically well-placed screws of 69%-94% for FH, 81%-100% for NV, and 85% to 98% for RG are found[6,10–15], with significant differences among subgroups of various NV devices.[16]

While there is some evidence that RG and NV lead to higher radiological accuracy than freehand (FH) instrumentation [12,16–21], this may not translate directly to real-world clinical benefits, especially in light of the high acquisition and maintenance costs inherent to these systems.[22] A recent systematic review on the cost-effectiveness of RG concluded that, although the technology is often claimed to be cost-effective, there appears to be a lack of published data to warrant this statement.[22] Possible benefits could include shorter operating times, and decreased incidences of radiculopathy and costly revision surgery for screw malposition, although the current level of evidence is very low, and there are no large prospective controlled studies comparing clinically relevant outcome such as pedicle screw-related revision surgery, as opposed to radiological surrogate measures alone.[5,6,14,21–30]

Currently, few published studies compare these techniques in a prospective setting, although they often suffer from insufficient power to demonstrate any potential clinical benefits, or report major conflicts of interests. Furthermore, while many studies compare RG to FH, there are no powerful studies comparing RG and NV.[5] We aim to conduct a prospective observational controlled study comparing RG, NV, and FH to create real-world evidence on these instrumentation techniques.[31]

Methods and Analysis

Study Design

The European Robotic Spinal Instrumentation (EUROSPIN) study is a prospective, international, multicentre, pragmatic, open-label, non-randomized, observational controlled study comparing the effectiveness of three techniques for pedicle screw instrumentation, namely RG, NV (CT-, O-Arm, or 3DFL-based), and FH.[31–33] Following the baseline evaluation, patients receive pedicle screw fixation by the senior surgeons on the author's list, and are subsequently followed up for 24 months. The primary analysis is conducted using the 12-month data. The study is designed to evaluate the superiority of RG and NV over FH in terms of the time to revision surgery for a malpositioned or loosened pedicle screw within the first postoperative year. This study protocol is compiled according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement.[34] Thirteen European centers from the Netherlands, Switzerland, Germany, Austria, and France participate in recruitment. Most centers contribute to at least two of the three study arms.

Study Population

Inclusion Criteria

Patients with the following indications for thoracolumbar pedicle screw placement are considered for inclusion: Degenerative pathologies (spinal stenosis, spondylolisthesis, degenerative disc disease, recurrent disc herniation), infections, vertebral tumors, as well as traumatic and osteoporotic fractures. Patients are required to give informed consent. Only patients aged 18 or older are considered for inclusion.

Exclusion Criteria

Patients undergoing deformity surgery for scoliosis or kyphosis are not eligible. Patients undergoing surgery at more than 5 vertebral levels are also not eligible.

Patient and Public Involvement

Patients were not involved in the development of the research question or study design, and will not be involved in recruitment or conduct of the study.

Study Procedures

Participating surgeons screen all patients with an indication for thoracolumbar pedicle screw placement for eligibility during the first consultation. If eligible, the patient receives an informative letter containing details on the EUROSPIN study after surgical consent has been given, including risks and benefits of participation. If written informed consent for study participation is given, the clinician or study nurse records baseline data. At this first visit, group allocation is determined.

Group Allocation

This is a non-randomized study. In this study, patients are not randomly allocated to treatment and control groups. Instead, patients undergo pedicle screw placement with the technique that the treating surgeon is most experienced with, and for which equipment is available at the center.[31] One reason concerns the surgeons' level of experience with a particular technique.[14,27,35,36] Because it has been demonstrated that the learning curve for some instrumentation techniques is steep, we did not deem it rational to have surgeons carry out procedures with a technique that they are not experienced with.[37] Instead, surgeons carry out the procedures with the technique that they are highly experienced with. This allows us to compare true effectiveness, similar to a prospective registry, as opposed to efficacy.[33] We have not implemented a pre-study "learning curve" phase, accordingly. A second reason is recruitment. Although some randomized controlled trials on robotic guidance in spinal instrumentation have been successful [14,38,39], they have suffered from rather slow recruitment and consequently relatively low power to demonstrate differences in an infrequently occurring endpoint, such as our primary endpoint. Multiple initialized randomized studies even had to be closed prematurely due to slow recruitment.[29]

Blinding

This is an open-label study. Both patients and treating physicians are aware of group allocation. However, the primary analysis is carried out by an epidemiologist blinded to group allocation, according to the pre-specified statistical protocol. Rating of CT images is carried out by independent radiologists blinded to group allocation.

Treatment Groups

Experimental Intervention I: Robot-guided pedicle screw placement

Robotic guidance in the form of the following systems is applied: Mazor X, Renaissance, or SpineAssist (Mazor Robotics, Ltd., Ceasarea, Israel) or ROSA Spine (Zimmer Biomet, Warsaw, IN, USA).[5,6,14,25,26,28] Fluoroscopic control is available.

Experimental Intervention II: Navigated pedicle screw placement

Navigated procedures are carried out under image guidance connected to a computer-assisted navigation system.[4,5,23] Preoperative or intraoperative image acquisition by spiral CT, cone-beam CT (O-Arm), or three-dimensional isocentric flurosocopy (3DFL) is applied for navigation.[4,5,23,40–42] Fluoroscopic control is available.

Control Intervention: Freehand pedicle screw placement

Conventional freehand surgery was chosen as the comparator because it is currently the most widely used and accepted standard technique around the world.[2] Freehand procedures are carried out according to surgeon preference, under fluoroscopic control.[5,14,19,23,25,26,28,40] Computer assistance is not available.

Cointerventions

Analgesic medication is available to the patients, if necessary. In addition, patients are able to undergo any further desired cointerventions such as elastic corsets or rigid casts, physiotherapy, or others.

Prognostic Factors

At the baseline assessment, patient age, height, weight, BMI, history of back or leg pain in months, prior surgery at any of the index levels, as well as highest level of education (elementary/high school/higher education/(post-)doctoral) and type of work (employed/self-employed/housework/student/retired/unemployed) are recorded. We also assess the use of analgesic medication (daily/at least once a week/not regularly) including over-the-counter drugs, patient satisfaction with current symptoms on a 3-step Likert scale (satisfied/neutral/dissatisfied), smoking status (active smoker/ceased/never smoked), and working status (able to work/unable to work/not applicable). Documented osteoporosis with or without treatment is recorded, as well as any procedures for osteoporotic fractures.

Outcome Measures

Primary Endpoint

We defined the primary endpoint as time to revision surgery for a malpositioned or loosened pedicle screw within the first postoperative year. In patients who experience the primary endpoint, CT imaging is carried out before revision surgery, and the degree of malposition is graded according to the classification described by Gertzbein and Robbins.[43]

Secondary Endpoints

A range of secondary endpoints is assessed. The following patient-reported outcome measures (PROMs) are captured at baseline and follow-up: Numeric Rating Scales (NRS) for back pain severity (NRS-BP) and leg pain severity (NRS-LP), as well as validated translations of version 2.1 of the Oswestry Disability

Index (ODI) for subjective functional impairment, and the three-level version the EuroQOL 5-dimensions (EQ-5D-3L) questionnaire (EQ-5D index and thermometer) for health-related quality of life (HRQOL).[44] The EQ-5D index is evaluated according to the respective national tariffs.[45] The proportion of patients in which revision or redirection of a pedicle screw was required intraoperatively (*intraoperative revision*) is recorded, as well as the number of instrumented index levels per patient. We record whether the procedure was carried out in a minimally invasive or open approach, and capture duration of the procedure in minutes, total intraoperative fluoroscopic radiation dose as dose area product (DAP) in mGy × cm^2, estimated blood loss in mL, need for blood transfusion, as well as any intraoperative or postoperative adverse events. We also record the level of experience of the surgeon placing the pedicle screws (resident/fellow/board-certified ≤ 10 yrs./board-certified > 10 yrs.). Conversions from one study arm to another, as well as from minimally invasive to open surgery are tracked. All serious adverse events (SAEs) are reported to the principal investigators' site.

Follow-Up

Patients undergo an "early" follow-up at one to three months. Subsequently, patients are followed-up at 12 months and 24 months postoperatively (Table 1). At follow-up, PROMs, use of analgesic medication, satisfaction with symptoms, smoking status, time to return to work in weeks, as well as any reoperations are captured.

Data Collection

Data are collected using a validated, secure web-based electronic data capturing system (CASTOR EDC, Amsterdam, The Netherlands). Each center is able to enter anonymized data into an Electronic Research Form (eCRF). Investigators from each center assign identifiers to patients, and store demasking lists. For follow-up of patient-reported outcome measures (PROMs), centers also have the option of dispatching standardized, scheduled surveys directly to the patients.[46] All data handling (data entry, storage, and

analysis) is confidential and complies with data protection regulations of participating countries and the European Union. Deidentified data is stored for 15 years.

Sample Size Calculation

It was determined that, to detect an absolute intergroup difference of 5% in the primary endpoint, 205 patients are required per group to achieve a power of $1 - \beta = 0.8$ at $\alpha = 0.05$.[47] Recruitment for a specific arm is stopped once the 205 patients have been included. The incidence rates are based on the published literature, with an approximated incidence rate of the primary endpoint of approximately 0% for the intervention and 5% for the control group.[5,6] Because the study protocol is in line with the normal clinical follow-up protocol of most centers, a low dropout rate is expected. This leads to a minimum total sample size of 615 patients.

Statistical Analysis

Overview

All analyses are carried out in R (The R Foundation for Statistical Computing).[48] A $p \leq 0.05$ on two-tailed tests is considered statistically significant. The primary analysis, conducted on the 12-month data, is carried out according to the intention-to-treat principle, with the intention-to-treat definition applying to the index surgery.[49] Results are reported as effect size estimates and their 95% confidence intervals.

Analysis of Primary Endpoint

The effect on the primary endpoint is reported as hazard ratios and their 95% confidence intervals, calculated from crude and adjusted Cox proportional hazards models. The crude model is considered the primary analysis. The primary endpoint is specified as the dependent variable, and group assignment as the independent variable, with the FH group as the reference category. Our null hypothesis is that neither RG nor NV lead to a significant decrease in the primary endpoint incidence compared to FH. Patients

who do not experience a primary endpoint are censored at the 12-month follow-up, with respect to the primary endpoint only.

Analysis of Secondary Endpoints

PROMs (NRS-BP, NRS-LP, ODI, EQ-5D) are analysed using baseline-adjusted linear mixed models. The mean overall effect over time, as well as effects at the specific follow-up timepoints, are estimated. The proportions of patients achieving MCID for each PROM, as well as proportions of patients reporting satisfaction, return to work, reoperations, and using analgesic medication are reported. MCIDs for the ODI, NRS-BP, and NRS-LP are defined as a reduction of ≥ 30% according to Ostelo et al.[50] The MCID threshold for the EQ-5D is set to 0.2 points according to Asher et al.[51] Return to work and overall reoperations are statistically analysed using crude and adjusted Cox proportional hazards models. In addition, intergroup comparison is performed for patient satisfaction and use of analgesic medication by logistic regression.

Subgroup Analysis

Prespecified subgroup analyses of the primary outcome are performed in the intention to-treat population to test for an interaction between study group and the subgroup variable. Stratified analyses are performed by indication for surgery, specific device used [16], type of exposure, as well as single-level or multi-level fusion.

Monitoring

Monitoring is performed according to the pre-specified monitor plan. An epidemiologist from the sponsor institution organizes an initiation monitor visit at every participating center before starting recruitment. This monitor visit checks whether all study staff are properly trained and the delegation of tasks are well documented (complete Investigator Site File, training and delegation logs). An additional audit is carried out at 6 months after initiation of recruitment to check whether source documentation and eCRF

documentation is similar. Throughout the entire study, additional queries by the monitor are sent to the investigator in the data capturing system to ensure proper data capturing.

Expected Completion

Recruitment is expected to be completed by January 2021, with the 2-year follow-up period extending to January 2023 for the final results.

Ethics and Dissemination

Ethical Approval and Study Registration

The study protocol is approved by the appropriate national and local authorities. Written informed consent is obtained from all participants. This study is registered at ClinicalTrials.gov under the identifier NCT03398915.

Dissemination

The final results will be published in an international peer-reviewed scientific journal, and communicated to study participants. No interim analyses have been specifically planned. To avoid any bias, the results of any interim analyses are neither shared with the investigators nor published until recruitment has been completed. There are no further restrictions to publication.

Discussion

The EUROSPIN study is a large, multicentre, pragmatic study that is aimed at resolving the discussion on whether computer assistance in thoracolumbar instrumentation leads to measurable and clinically relevant improvements in patient-reported clinical outcome or complication rate.

Previous studies have created some evidence that both robotic guidance and navigation lead to a somewhat higher radiological accuracy than freehand pedicle screw insertion, with inconsistent results at a rather low level of evidence [12,14,16–21,23]. It is still unclear whether this increased radiological accuracy, usually measured as the degree of deviation from the desired transpedicular trajectory, translates to a clinical benefit to patients. It is hypothesized that, when using computer assistance, the lower rate of pedicular cortical encroachment leads to a lower incidence of radiculopathy [24,52], thus preventing revision surgery [6], decreasing overall treatment costs [53], and improving overall patient-oriented outcomes.[38] A meta-analysis has demonstrated that both robotic guidance and navigation lower the incidence of revision surgery for malpositioned pedicle screws.[5] However, the rate of intraoperative screw revisions was markedly but not statistically significantly increased, the quality of the included individual studies was low, and it was determined that prospective studies assessing this research question with larger sample sizes are necessary to draw conclusions.[5] In addition, there are only very few, small studies comparing robotic guidance to navigation directly.[29,54] For these reasons, we designed our study to address these biases, and to provide higher-level evidence on clinical questions, comparing all three concepts of pedicle screw placement.

A specific goal of the EUROSPIN trial is to avoid potential conflicts of interest.[55] Therefore, we decline any sort of direct involvement and study-related financial support by the industry, and aim to minimize personal conflict of interests with device manufacturers. This may enable execution and critical appraisal of the study results with less bias.[55,56]

The study has some limitations. First, for logistical and practical reasons, not all sites are able to contribute to all three study arms. This may create center bias. However, the rationale for this design is to prospectively collect data obtained from surgeons experienced with the three techniques, resulting in a design similar to a prospective multicentre registry. Furthermore, we are unable to conduct a detailed evaluation of cost-effectiveness. The cost-value relationship of robotic and intraoperative imaging systems remains controversial, and it is as of yet unclear if there are any demonstrable clinical benefits that warrant the high acquisition and maintenance costs inherent to these systems.[22] In addition, preoperative radiation that may be required for surgical planning may differ among the groups, and is not captured. In this light, it is important to consider that, even if the navigated and robotic techniques would result in decreased intraoperative radiation, this benefit to the patient may be levelled out by the additional radiation dose necessary for planning.

Furthermore, although all participating surgeons are experienced with the respective techniques applied, as we do not specify a minimum case number for participating surgeons, surgeon experience may constitute a potential bias. We aim to correct for this potential bias by collecting data on the degree of experience of the surgeons placing the pedicle screws, which allows for statistical adjustment if necessary. Another potential limitation exists in the fact that thresholds for revision of a malpositioned or loosened screw may vary among centers and surgeons. Moreover, our study is likely underpowered for subgroup analyses analysing treatment effects among the single devices and the different indications for surgery. Lastly, some potential confounders such as comorbidities and symptom duration are not collected.

Patients are not randomly assigned to treatment groups in the EUROSPIN study. As detailed above, there are two main reasons that randomization was deemed disadvantageous in this specific study. First, most centers do not have both a robotic system and conventional neuronavigation available, making it impossible to randomize to all three groups at every center. Furthermore, we aim to have the surgeons

perform the procedures with the technique they are most experienced with.[27,31,36] This enables us to compare the treatment modalities in a more clinically applicable scenario, assessing effectiveness instead of study-specific efficacy, similar to a prospective registry.[33] Accordingly, no "learning curve" phase was implemented. Even for randomized studies, Devereaux et al. suggest that surgeon-based or "expertise-based" group assignment, in which patients are not randomized to treatments but rather to clinicians experienced with a certain treatment, may lead to greater real-world applicability of study results.[31] In addition, some commenced randomized trials comparing robotic surgery with conventional techniques have had to be declared futile due to slow recruitment, usually because of a patient preference towards newer techniques. A split design, similar to the Spine Patient Outcomes Research Trial (SPORT), with a randomized and non-randomized subgroup was available as an alternative.[57] However, due to the aforementioned logistic difficulties and possible bias in experience, we have decided upon a simple, registry-like design for the EUROSPIN study.

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Tables

Table 1 Chart demonstrating items collected at baseline and follow-up.

Item	Baseline	Surgery	Discharge	1 to 3 months postop.	12 months postop.	24 months postop.
Informed consent	X					
Group allocation	X					
Demographics	X					
Surgeon experience		X				
Surgery		X				
Intraoperative parameters		X				
Perioperative parameters		X	X			
Blood transfusion		X	X			
Length of stay			X			
ODI	X			X	X	X
NRS-BP + NRS-LP	X			X	X	X
EQ-5D-3L	X			X	X	X
Satisfaction (Likert)	X			X	X	X
Work status	X			X	X	X
Smoking status	X			X	X	X
Use of analgesia	X			X	X	X
Intraoperative screw revision		X				
Revision surgery for screw malposition or loosening	With occurrence					
Computed tomography	With occurrence of revision surgery					
Adverse events	With occurrence					
Reoperations	With occurrence					
Other treatments	With occurrence					

EQ-5D-3L, 3-level version of the EuroQOL five-dimensions questionnaire; NRS-BP, numeric rating scale for back pain severity; NRS-LP, numeric rating scale for leg pain severity; ODI, Oswestry Disability Index;

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract
	2b	All items from the World Health Organization Trial Registration Data Set	WHO Supplement (only for editors)
Protocol version	3	Date and version identifier	WHO Supplement (only for editors)
Funding	4	Sources and types of financial, material, and other support	3-4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3
	5b	Name and contact information for the trial sponsor	4
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	3-4
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8, Registration
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10,11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11,12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12,13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12,13
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12,15

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	3,4
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A, WHO supplement
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not provided
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.