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ABSTRACT

INTRODUCTION: Lumbosacral radicular syndrome is often caused by a disc herniation. The standard surgical technique to remove a disc herniation is open microdiscectomy. An alternative technique is Percutaneous Transforaminal Endoscopic Discectomy (PTED), which is less invasive. In The Netherlands, PTED is not currently considered standard care and therefore, not reimbursed within public health insurance. A pragmatic, multi-centre, non-inferiority, randomised controlled trial has been designed to determine the effectiveness and cost-effectiveness of PTED versus open microdiscectomy for the treatment of a lumbar disc herniation.

METHOD AND ANALYSIS: In total, 682 patients between 18-70 years of age with > 10 weeks of radiating pain or with > 6 weeks of excessive radiating pain are to be recruited from participating centres. Patients must have an indication for surgery based upon an MRI demonstrating compression of the nerve root from a lumbar disc herniation. Patients are to be randomised to PTED or open microdiscectomy. The primary outcome is self-reported leg pain measured by the 0-100 mm Visual Analogue Scale. Secondary outcomes include self-reported health and functional status; back pain; self-perceived recovery; and a physical examination. Outcomes will be measured the day following treatment and at 2, 4, and 6 weeks, and 3, 6, 9, 12 and 24 months. Physical examination will be performed at 6 weeks, and 3 and 12 months. An economic evaluation will be performed from a societal perspective and cost-questionnaires will be used (e.g. EQ-5D-5L). The data will be analysed longitudinally; the non-inferiority margin for the primary outcome is 5. Bootstrapping techniques will be used for the economic evaluation.

ETHICS AND DISSEMINATION: This study has received approval of the Medical Ethical Committee of the VU Medical Centre Amsterdam: NL50951.029.14. The results will be published in an international peer reviewed scientific journal.

REGISTRATION: This trial is registered at ClinicalTrials.gov: NCT02602093.

Strengths and Limitations

- Large, multi-centre, pragmatic, randomised controlled trial
- Use of standardized and validated outcomes instruments
- Data are to be analysed longitudinally and multi-level
- Inclusion of an economic evaluation
- Potential performance bias due to lack of blinding of patients and providers

INTRODUCTION

Lumbosacral radicular syndrome is a common health problem with a lifetime prevalence that varies from 12.2% to 43% and has a point prevalence ranging from 1.6% to 13.4%.[1-6] Lumbosacral radicular syndrome is often caused by a lumbar herniated disc[7] and is associated with a greater incidence of sickness benefit,[8] increased pain and disability, and poorer quality of life[9] than those with non-specific low-back pain. In cases of a disc herniation, lumbosacral radicular syndrome can be treated either conservatively or surgically.[7]

To remove the disc herniation, the standard surgical technique is open microdiscectomy. A more recently developed technique is percutaneous transforaminal endoscopic discectomy (PTED). In short, open microdiscectomy is performed under general anaesthesia and surgeons operate with a direct vision on the herniated disc, while PTED is conducted transforaminally and these patients undergo local anaesthesia and

surgeons operate through a working cannula with an indirect vision via an endoscope. Based upon the current literature, PTED is a safe method for the removal of a lumbar disc herniation.[10] Possible benefits of PTED versus open microdiscectomy are: 1) Decreased medical costs because patients are treated on an outpatient basis; 2) It is easier to remove intra- and extra-foraminal herniated discs; 3) There is less chance of scar formation; and 4) The technique is potentially more effective for obese patients. However, too few, large prospective studies have examined this in detail, therefore, the benefits may be speculated.[11-13]

Despite that PTED is becoming more commonly used, there are still questions regarding its effect and the associated costs.[11, 13, 14] A recent systematic review[11] identified three randomised controlled trials (RCTs), which examined the effect of PTED compared to open microdiscectomy.[15-17] Their results suggest that there is low to very low quality evidence that PTED is no more effective than open microdiscectomy for self-reported back pain, leg pain, functional status, recovery, return-to-work, and satisfaction with surgery. Importantly, all three studies were of poor methodological quality and examined relatively few patients (i.e. ranging from 40 to 60 individuals). A more recent study concluded that PTED shows similar results compared to open microdiscectomy.[13] However, this was a single-centre study; it was conducted by a surgeon with a keen interest in the results of PTED; it included patients over a long period of time (i.e. the study started in 2006 and was published in 2017) suggesting possible selection of patients included in the trial; and the inclusion criteria published in the original protocol were different from those in the final publication. Additionally, the economic evaluation of this study has not yet been published.[18] This makes it difficult to assess the cost-effectiveness. Therefore, discussion regarding the effectiveness and cost-effectiveness of PTED remains.

In The Netherlands, the effectiveness of PTED has been heatedly debated. According to the Dutch Health Care Institute, a new surgical technique must meet certain requirements in order to be reimbursed by the public health system. The Health Care Institute promotes the quality of Dutch Health Care and advises the Ministry of Health, Welfare and Sport on the content of the public health insurance. Based on a review,[11] the Health Care Institute claimed there is insufficient evidence for PTED to be included for reimbursement from the public health insurance package and as a result, patients are forced to pay the costs of treatment out-of-pocket. In order to deal with this issue and to answer the remaining questions about PTED, this large, pragmatic, methodologically rigorous multi-centre study has been designed.

This study is expected to have a major societal impact because it will determine if PTED should be included in the Dutch health insurance package. Furthermore, this study will provide more insight in PTED internationally, resulting in improved care for patients with a lumbar disc herniation. The primary hypothesis of this study is that PTED is not less effective and not less cost-effective compared to standard care (i.e. open microdiscectomy) for patients with symptomatic, lumbosacral radicular syndrome as a result of a lumbar disc herniation. Therefore, a non-inferiority design will be used.

METHOD AND ANALYSIS

Study design

A pragmatic, multi-centre non-inferiority randomised controlled trial (RCT) will be used. Following the baseline measurements, wherein clinical and socio-demographic measurements will be collected, patients are to be

randomised to one of two groups: the control group will receive standard open microdiscectomy and the intervention group will receive PTED. Patients will be followed for two years, but the primary analysis will be conducted on the one-year data.

Important protocol modifications will be registered at ClinicalTrials.gov and communicated to all relevant parties involved in this study (Medical Ethical Committee, ZonMw, included patients, participating surgeons, and members from the advisory board (listed in the acknowledgments)).

Study population

In total, 682 patients with a magnetic resonance imaging (MRI) confirmed lumbosacral radicular syndrome, due to a lumbar disc herniation are to be recruited. Patients will be recruited from five hospitals and one private health clinic located in Arnhem/Zevenaar, Leiderdorp, Tilburg and Rotterdam (The Netherlands). Each patient is required to sign a written informed consent prior to participation. If patient recruitment is slower than planned, (one or two) additional hospitals may be recruited.

In order to be eligible to participate and in accordance with the Dutch Guideline Lumbosacral Radicular Syndrome,[19] a subject must meet all of the following conditions:

Inclusion criteria

- 18-70 years of age;
- > 10 weeks of radiating pain with or without motor or sensory loss in the leg, or with > 6 weeks of excessive radiating pain and no tendency for any clinical improvement;
- Indication for surgery;
- MRI demonstrating lumbar disc herniation with nerve compression with or without concomitant spinal or lateral recess stenosis or sequestration;
- Sufficient knowledge of the Dutch language in order to complete forms and follow instructions independently.

Exclusion criteria

- Previous surgery on the same or adjacent disc level;
- Cauda equina syndrome;
- Spondylytic- or degenerative spondylolisthesis;
- Pregnancy;
- Severe comorbid medical or psychiatric disorder (American Society of Anaesthesiologists >2);
- Severe caudal or cranial sequestration;
- Contra-indication for surgery;
- Moving abroad at short notice.

Study procedures

Participating surgeons will screen all eligible patients with a lumbar disc herniation during the consultation (Table 1). If eligible for inclusion, patients will receive information relevant to the study by means of a letter. Dutch law requires that patients are given at least two days to consider participation. Following this initial

screening, the patient is to be examined by a trained research nurse and the informed consent is obtained; baseline measurements are performed; and patients are randomised.

Randomisation

Patients will be randomised in a 1:1 ratio to PTED or open microdiscectomy. An experienced statistician prepares computer-generated, random number tables. Treatment allocation will be concealed. The key will be withheld from all participants and researchers involved in this study. Variable block sizes of 4, 6 and 8 are used and stratified by treatment centre. The random-number tables are to be entered into a computer system by an independent software company, and allocation will be performed by the computer system once baseline data and physical examination are obtained from an independent research nurse responsible for the treatment allocation.

Blinding

No attempt will be made to blind the patients. Blinding is considered impossible, because the procedures are fundamentally different. Furthermore, outcomes assessors cannot be blinded, given that the primary outcomes are all self-reported. The analysis will be performed blinded for treatment allocation.

Treatment

Intervention: Percutaneous transforaminal endoscopic discectomy (PTED)

PTED is to be conducted as follows:[20] local anaesthesia is to be administered and consists of light sedation with dexmedetomidine or a combination of propofol and remifentanyl for the convenience of the patient. The amount of administered sedation should still allow the patient to respond to nerve root manipulation. Verification of the site is to be performed by an image intensifier using fluoroscopy (anteroposterior and lateral view) and is depending upon the patient's posture. An incision just above the dorsolateral side of the pelvis is conducted, where a needle is to be set from the incision to the superior articular process of the lower involved vertebrae of the herniated disc. Position will be checked again under fluoroscopy. After the needle has reached the superior articular process, a guide wire is to be inserted. Following that, a series of conical rods are to be introduced, subsequently a drill/reamer is to be introduced through the cannula and rods. After drilling through the superior articular process is conducted in order to enlarge the neuroforamen, the instruments are to be removed, but the guidewire is left in place and the endoscope with the working channels are to be introduced via an 8 mm cannula. The image intensifier ensures that the position of the cannula is maintained. Following removal of the disc herniation with a rongeur, the cannula and endoscope are removed. The patient is to be treated on an outpatient basis.

Comparison: Open Microdiscectomy

Open microdiscectomy is to be conducted as follows: general or spinal anaesthesia is to be administered. Verification is to be performed using a fluoroscopy and the patient is to be positioned prone or in the salaam position. Loupe or microscope magnification may be used according to the surgeon`s preference. A paramedian incision is to be performed and the level is to be indicated. Following the identification of the lamina, the yellow ligament will be removed to identify the nerve root and disc herniation. Laminotomy as well as foraminotomy is to be performed, if necessary. The amount of degenerative disc material shall be removed at the discretion of

the attending surgeon. Post-operative policy will be followed and it is expected that the duration of recovery in the hospital may vary from 1-2 days, but the patient will be discharged as soon as medically responsible.

Co-interventions

Pain medication will be offered to patients, should this be necessary. In addition, use of co-interventions will be monitored by self-reported cost questionnaires, in which medication usage and any health care utilization is recorded throughout the follow-up period.

Learning curve

It will be necessary to train surgeons in the use of PTED because prior to the start of this study only two surgeons in The Netherlands were proficient in this technique. One of these surgeons is participating in this study (BSH). This experienced surgeon will provide the training to the other surgeons, all of who have more than ten years of surgical experience. The initial training will be first conducted on cadavers, and only once the surgeons are comfortable with the use of the procedure, will they perform this technique on patients under the tutelage of the PTED-experienced surgeon. It is expected that 50 patients per surgeon will be necessary to become proficient in PTED (defined as the 'learning curve'). Thus, 150 PTED patients will be registered as learning curve patients, and included in the study; however, they will not be included in the primary analysis. Additionally, competency in the use of PTED by the surgeons is to be evaluated using skill-based questions measured by a Likert-scale and the Objective Structured Assessment of Technical Skills (OSATS). These will be recorded and evaluated by both the teaching surgeon as well as the surgeons undergoing the training.[21]

Prognostic factors

The following potential prognostic factors are to be measured: 1) socio-demographic characteristics (e.g. age, gender); 2) characteristics of the complaint (e.g. duration and severity); 3) baseline pain and functional disability; 4) lifestyle factors (e.g. smoking and alcohol use); 5) psychological factors (e.g. expectations of recovery, emotional well-being; 6) psychopathology as measured with the four dimensional symptom questionnaire (4DSQ; dimensions: distress, depression, anxiety and somatization);[22] 7) work-related factors (e.g. physical workload, job satisfaction); and 8) previously received treatment due to the same episode of back complaints (e.g. medication and physiotherapy).

Outcome measurements

The outcomes are to be measured by validated self-reported questionnaires and by physical examination. Data are to be collected prior to randomisation (baseline), the day following surgery, at 2, 4, and 6 weeks, and at 3, 6, 9, 12, and 24 months following surgery (Table 1).

All questionnaires will be sent automatically by e-mail with a personal link to the digital questionnaire. If necessary, a reminder will be sent after 3 days; after six days the research nurse will call the patient with the request to fill in the questionnaire. Patients who deviate from the original protocol will be registered and will be asked to continue filling in the self-reported questionnaires.

Primary outcomes

The primary outcome, leg pain, is to be measured by the Visual Analogue Scale (VAS; scale 0-100 mm). This outcome measure has been identified in a systematic review to be one of the most commonly measured outcomes, and is specific and responsive to change in a population undergoing lumbar spine surgery.[23]

Secondary outcomes

Functional status: will be measured with the Oswestry Disability Index (ODI). The ODI[24] is one of the principal condition-specific outcome measures used in the management of spinal disorders. The current version of the ODI (2.1a) is to be used.[25] The ODI has been extensively tested and showed good psychometric properties.[26]

Low-back pain: will be measured with the VAS (scale ranging from 0mm (no pain) to 100mm (worst imaginable pain)).

Generic quality of life: will be measured with the Dutch version of the short form SF36. The SF-36 questionnaire has been validated and found reliable for low back pain.[27] The questions are divided into eight domains: 1) physical functioning, 2) physical role limitations, 3) emotional role limitations, 4) social functioning, 5) physical pain, 6) general mental health, 7) vitality, and 8) general health perception. Per domain the scores of the items are added up and transformed into a scale of 0 to 100. A higher score reflects a better health condition. In addition, these eight domains can be summarized in a physical and psychological main domain.

Self-perceived recovery of the patient: will be measured with a seven-point Likert-scale. The score on this scale varies from 'completely recovered' to 'worse than ever'. We will dichotomize the outcome with 'completely recovered', 'moderately recovered' and 'a bit recovered' as 'recovered' and the other four categories as 'not recovered'.

Patient satisfaction: will be measured using the Likert-scale, Body Image and the Cosmesis scale.[28, 29] Body satisfaction will be measured using a four-point Likert-scale (ranging from 'not at all', 'a little', 'quite', to 'yes, very much'). Satisfaction change of complaints and satisfaction treatment will be measured using a seven-point Likert-scale (ranging from 'completely satisfied with current symptoms' to 'completely dissatisfied with current symptoms'). The scales will be completed by the patients prior to and following surgery. Scar satisfaction will also be measured using the seven-point Likert-scale and with a 1-10 numeric rating scale (ranging from 1 = 'as ugly as conceivable' to 10 = 'almost no scar perceived').

Physical examination: will be performed at 6 weeks, 3 and 12 months following surgery. This will include: scar size; patellar and achilles tendon reflexes; straight leg raising test; cross straight leg raising test; finger-floor distance; strength measurement of the quadriceps using the Medical Research Council (MRC); sensibility dermatomes L1-S1, abdominal muscle strength; and patients' weight. The patellar and tendon reflexes are to be measured in a sitting upright position with both feet dangling above the ground. Tendon reflexes are tapped up to a maximum of two times with the reflex hammer. Reflexes are distinguished into absent, reduced, normal, increased, and clonus reflexes. The straight leg raising test and cross straight leg raising test are both measured as negative when no shooting leg pain is perceived, and positive when shooting pain is perceived. Finger-floor distance is the distance between the longest finger and the floor when the patients perform a forward bent with the knees extended. Muscle strength of the quadriceps is measured from a sitting position. Patients will be

asked to extent their knee while the research nurse exerts counter-pressure just above the ankle. Muscle strengths are rated on the Dutch version of the MRC, ranging from 0= no contraction to 5 = normal muscle strength). For the sensibility the research nurse checks every dermatome area (L1-S1) by touching the patient with a sharp and blunt object. Patients indicate with their eyes closed when sensation is felt. Sensibility varies from decreased, normal or increased sensibility compared to the other leg. Abdominal strength is measured by counting the maximal number of abdominal crunches from the supine position. Patients are asked to reach the hands towards the bended knees and to lift the scapulae from the surface. At any time, the lumbar spine will be supported by the underlying surface to minimalize the range of motion of the lumbar spine. Without an increase of pain the maximum is set at a cut-off point of 26 crunches.

Screening and operation case record forms are to be completed by the surgeons, while discharge forms, physical examination and baseline intake forms are to be completed by a trained research nurse.

Table 1. Flowchart visits and case report forms

Visits and Case report forms	Intake + baseline	Surgery	1-2 days following treatment	2 weeks following treatment	4 weeks following treatment	6 weeks following treatment	3 months following treatment	6 months following treatment	9 months following treatment	12 months following treatment	24 months following treatment
Surgeon visit	X					X*					
Informed consent	X										
Research nurse visit	X					X	X			X	
Randomisation	X										
Surgery		X									
Discharge		X**	X**								
Four-Dimensional Symptom Questionnaire (4DSQ)	X										
Oswestry Disability Index (ODI)	X		X	X	X	X	X	X	X	X	X
Cost questionnaires	X			X	X	X	X	X	X	X	
EuroQol (EQ-5D-5L)	X		X	X	X	X	X	X	X	X	X
VAS leg pain, VAS Back pain	X		X	X	X	X	X	X	X	X	X
Quality of Life VAS	X		X	X	X	X	X	X	X	X	X
Patient self-perceived recovery and satisfaction			X***	X	X	X	X	X	X	X	X
Short Form 36 (SF36)	X			X	X	X	X	X	X	X	X
Physical examination	X					X	X			X	
Revisit and complications	With occurrence										

* 6 weeks visit may be performed also by the research nurse depending on the normal protocol hospital.

** Discharge form will be filled in depending on discharge moment.

*** Only self-perceived recovery is measured not self-perceived satisfaction.

Complications, operative morbidity, and re-operations

Immediately following surgery and discharge, the surgeon and research nurse will perform a systematic assessment of complications (including urinary tract infection, secondary bleeding, and progressive neurological deficit). In addition, surgeons will record any perioperative complications like cerebrospinal fluid leakage, nerve root damage, and if the surgery was initiated at the wrong disc level. Re-operation at the initial site is to be considered a poor outcome. Re-operation in both groups will be recorded. Perioperative morbidity will be assessed with operation time, perioperative blood loss, hospital stay and re-operative rate as related to the primary condition (lumbar disc herniation).

Sample size calculation

The mean difference and standard deviation (SD) for the VAS (leg pain) used in the sample size calculation was: mean 5; SD 14.9.[30] The margin of non-inferiority was set at 5, (one-sided) alpha at 0.05 and beta at 0.10 (power 0.9). We estimated that in total 306 patients are needed to demonstrate non-inferiority on the primary outcome. Accounting for 20% attrition, the aim is to recruit 382 patients. As the Ministry of Health in the Netherlands has stipulated that PTED will only be reimbursed if patients participate in the randomised trial, an extra 300 patients will be necessary for the inclusion of 150 patients in the PTED learning curve. Consequently, a total of 682 patients will be recruited for this study. Patients are likely to participate in this study, because PTED will only be reimbursed by Dutch health care insurance for participants in this study. Therefore, reaching the target sample size is not likely to become a problem.

Data analysis

Data analysis will be conducted by a researcher or statistician blinded for treatment allocation after follow-up is finished. No interim analysis will be performed.

All data handling (entry, coding, storage and analysis) is confidential and complies with the Dutch Personal Data Protection Act. The anonymous data are stored in a central warehouse for at least 15 years.

Effect analysis

Characteristics of the patients will be presented using descriptive statistics (mean (SD), median (range) or proportion) to assess if balanced groups were obtained after randomisation. The non-inferiority margins are set and listed in table 2.

Table 2. Non-inferiority margins

Outcome measurements	Expected differences	Non-inferiority margin
VAS leg pain (0-100 scale)	<5 **	5
ODI (0-100 scale)	<5 *	5
VAS low back pain (0-100 scale)	<5 *	5
SF36 (0-100)	<5*	5
Self-perceived recovery (% 1 and 2 on the 7-point Likert-scale)	<10%***	5
Patient satisfaction (% 4 on the 4-point Likert-scale)	<5%	5
Patient satisfaction (% 1 and 2 on the 7-points Likert-scale)	<5%	5
Scar satisfaction (1-10 scale)	<1	0.5
Patellar reflex (% normal reflexes)	<5%	5
Achilles reflex (% normal reflexes)	<5%	5
Straight leg raising test (% negative tests)	<5%	5
Cross straight leg raising (% negative tests)	<5%	5
Finger floor distance (cm)	<5	5
Muscle strength quadriceps (% normal muscular strength)	5%	5
Sensibility dermatomes L1-S1 (% normal sensibility)	5%	5
EQ-5D-5L	<0.05****	0.05
Costs (healthcare perspective)	<$500,- ***	250
Costs (societal perspective)	<$1500,- ***	500

* Obtained from the literature [13, 30]
** Obtained from the literature [13]
*** Obtained from the literature [30]
**** Obtained from the literature [31]

The primary data analysis will examine the effects of PTED for leg pain for those patients not in the learning curve, and shall be conducted according to the intention-to-treat principle. If necessary, missing items will be imputed using multiple imputation techniques. Linear and generalized multi-level analyses will be used, accounting for dependency of measurements over time within patients and patients nested within the surgeons, thus representing a 3-level model: time, patient and surgeon in that order. The data are to be examined longitudinally and the primary analysis will be aimed at average differences in effectiveness between the two treatment modalities. We will also include treatment * time interactions to explore whether these effects are different over time. In addition to the crude analyses, all analyses will be adjusted for potential confounders, such as age, gender, nature and severity of the presenting complaint. In a secondary analysis, a per-protocol analysis shall be conducted. The secondary continuous outcomes, such as low-back pain, functional status, will be analysed similar to the primary data analysis; however, recovery and some of the physical performance measures (Table 2.) are to be treated as a dichotomous variable and will be analysed in logistic regression analyses.

Complications will be summarized for the time period of the study, but also presented for those complications encountered before and after 6 weeks.

Sensitivity analyses effect

Sensitivity analysis will be conducted in those patients with a) a paramedian/median disc herniation and b) a foraminal/extra-foraminal disc herniation. The latter is much less common, representing for approximately 7% to 12% of all lumbar disc herniations.[32] The goal of this analysis is to test the robustness of the data to changes

in underlying assumptions regarding the type or location of the hernia, and in this particular case, to determine whether the same effect is found for the subgroup with paramedian/median lumbar disc herniation as for the entire group. Finally, a sensitivity analysis will be conducted for all patients, including those in the 'learning curve' in order to determine if these outcomes are different than the primary analyses.

Results from all analyses will be expressed as mean effect estimate with 95% confidence intervals and these estimates will be subsequently compared to the margin of non-inferiority in order to make inferences about the non-inferiority of the intervention, PTED.

Economic evaluation

Both cost-effectiveness and cost-utility analysis will be conducted from a societal perspective alongside the RCT. We will measure, value and analyse total costs of all patients and relate the difference in costs to the difference in effects between the two groups.

Direct costs include costs of the interventions, hospitalisation after surgery, medication and other health care utilization. Patient costs and cost of productivity loss, absenteeism and presenteeism, will also be included. Health care utilization, patients cost and productivity loss will be measured using self-completed cost questionnaires. The cost of the interventions will be estimated using a bottom-up approach (micro-costing) and hospitalisation will be registered using case record forms. The Dutch tariff of the EQ-5D-5L[33, 34] will be used to calculate the quality-adjusted life years (QALYs). The EuroQol measures five dimensions: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. Each dimension consists of one item, while five levels are distinguished ('no', 'slight', 'moderate', 'severe problems', 'unable to do').

Costs resulting from productivity loss are to be estimated using the friction cost method, which assumes that sick workers are replaced after a period of time (12 weeks).[35] Mean productivity costs per working hour are to be adjusted for age and gender and used to estimate the cost of absenteeism. Health care utilization is to be valued according to the guidelines published in the updated handbook for economic evaluation in The Netherlands.[35] Medication is to be valued using prices from the Royal Dutch Society for Pharmacy.[36]

Cost-effectiveness analysis

Total costs will be related to the primary effect measure, leg pain. A cost-utility analysis will be performed with QALYs. From the EQ-5D-5L utilities will be obtained and QALYs will be calculated using linear interpolation between measurement points. The primary analysis will be conducted according to intention-to-treat. Missing data will be imputed using multiple imputation by changed equations.[37] Incremental Cost Effectiveness Ratios (ICERs) will be calculated by dividing the difference in costs by the difference in effects. We will perform a cost-effectiveness analysis with leg pain as outcome and a cost-utility analysis with QALYs as outcome. In order to account for the possible clustering of data, analyses will be performed using linear multilevel analyses.[38] Accounting for the possible clustering of data (e.g. at the hospital and surgeon level) is very important, as most economic evaluations fail to do so, whereas ignoring the possible clustering of data might lead to inaccurate levels of uncertainty and inaccurate point estimates.[38] Bias corrected and accelerated bootstrapping with 5,000 replications will be performed in order to estimate 95% confidence intervals around cost differences and the uncertainty surrounding the ICERs. Uncertainty will be shown in cost- effectiveness planes and cost-

effectiveness acceptability curves, and sensitivity analyses will be performed to test the robustness of the study results.[39-41]

Sensitivity analysis cost-effectiveness

Sensitivity analyses will be conducted for the most important cost drivers in order to determine the robustness of the findings. In addition, the main analyses are to be repeated using only complete cases (i.e. complete clinical outcome data and complete cost data). Lastly, the impact of the Human Capital Approach will be compared to the friction cost method approach. The Human Capital Approach evaluates the total costs of productivity loss without considering the possibility of replacing the sick worker.

ETHICS AND DISSEMINATION

This study has received approval of the Medical Ethical Committee of the VU Medical Centre Amsterdam and confirmation can be supplied upon request [corresponding number: NL50951.029.14; November 5, 2015]. Serious adverse events (SAE) and adverse events will be registered; SAE will be reported within 24 hours (see section 'complications, operative morbidity, and re-operations'). The sponsor (also) has an insurance, which is in accordance with the legal requirements in the Netherlands. The insurance applies to the damage that becomes apparent during the study or within four years after the end of the study. This study will be monitored according to a detailed monitoring plan adapted to the risk classification of the Dutch University Federation guidelines. Based on this guideline, the risk classification of this study is regarded negligible. Considerations in this assessment are that this is an investigator-initiated trial, not with vulnerable patients, and while side effects are known, such as nerve root damage, severe adverse events are extremely rare. Audits may be required by and will be granted to Medical Ethical Committee and regulatory authority inspections. Patients' permission for these audits is obtained with informed consent.

The final trial results will be communicated to participants, healthcare professionals, professional organisations and relevant guideline committees in the Netherlands. We will publish the results in an international peer reviewed open access scientific journal. There are no publication restrictions.

DISCUSSION

This large, multi-centre, pragmatic study will be conducted to resolve the discussion regarding the effects and costs of PTED compared to open microdiscectomy for patients with lumbosacral radicular syndrome caused by a lumbar disc herniation. At the moment, in the Netherlands PTED does not comply with standards of practice, and therefore, is not included in the current Dutch public healthcare package. The Dutch Ministry of Health classified PTED as an important technique to examine, but placed conditions on reimbursement of the intervention. Namely, patients must be included in the RCT in order to receive reimbursement. This presented a unique challenge for us because this means that all patients are to be included from the beginning while the surgeons who are not experienced in PTED are still undergoing the training, hence, the reason for the learning curve and the reason why these participants will be included in the study. Additionally, in order to prevent discussion regarding the effects of PTED following this study, a document was signed by all participating parties (e.g. professional surgical organisations, insurance companies, Dutch healthcare institute) to agree upon the study design and the criteria for in- or exclusion of PTED from the Dutch public healthcare package.

Since the trial was published in a trial registry (clinicaltrials.gov; November 2013), the protocol has been modified, namely a physical examination has been added in order to obtain more objective information regarding the physical rehabilitation, and a numeric rating scale (NRS) has been added in order to measure back, leg pain and quality of life. The reason for the latter is, the VAS may be completed by participants using different digital apparatuses (i.e. PC, tablet or mobile phone), with the result that the lengths of the VAS scale may vary. The validity and reliability is, therefore, uncertain. Based upon the literature, it would appear that the NRS and VAS demonstrate comparable values for pain following surgery;[42] however, the aforementioned issue, namely the use of the VAS on different digital apparatuses has not previously been examined. In order to determine whether this has bearing on the outcomes, a sensitivity analysis shall be conducted, and we will examine the correlation between the VAS and NRS.

The trial is an ongoing study and runs from February 2016 to February 2020.

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FOOTNOTES

Contributorship statement:

SH, JvS, WP, MvT, SR contributed to writing the proposal and acquiring the grant from The Netherlands Organisation for Health and Care Research (ZonMw). AS prepared the first draft of the study protocol. All authors (AS, PG, SH, JvS, WP, MvT, MdB, SR) contributed to the final design of this study protocol, assisted with drafting the manuscript, and approved the final version of the manuscript. MdB developed the statistical analysis plan.

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Competing interest statement:

The professional judgment concerning the primary interest (e.g. validity of the research) will not be influenced by a secondary interest. All authors have read and understood the BMJ policy on declaration of interests. We all declare that we have no competing interests other than receiving grants. For this particular study we had financial support from The Netherlands Organisation for Health Research and Development. We do not have relationships with any organisations that might have an interest in the submitted work. All authors have completed the ICJE uniform at www.icmje.org/coi_disclosure.pdf.

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Data sharing statement:
This article refers to a study protocol; data are not yet available. We will share all data through open access once the final results have been published.

Ethical approval: This study has received approval of the Medical Ethical Committee of the VU Medical Centre Amsterdam and confirmation can be supplied upon request [corresponding number: NL50951.029.14; November 5, 2015].

Table 1. Flowchart visits and case report forms

Visits and Case report forms	Intake + baseline	Surgery	1-2 days following treatment	2 weeks following treatment	4 weeks following treatment	6 weeks following treatment	3 months following treatment	6 months following treatment	9 months following treatment	12 months following treatment	24 months following treatment
Surgeon visit	X					X*					
Informed consent	X										
Research nurse visit	X					X	X			X	
Randomisation	X										
Surgery		X									
Discharge		X**	X**								
Four-Dimensional Symptom Questionnaire (4DSQ)	X										
Oswestry Disability Index (ODI)	X		X	X	X	X	X	X	X	X	X
Cost questionnaires	X			X	X	X	X	X	X	X	
EuroQol (EQ-5D-5L)	X		X	X	X	X	X	X	X	X	X
VAS leg pain, VAS Back pain	X		X	X	X	X	X	X	X	X	X
Quality of Life VAS	X		X	X	X	X	X	X	X	X	X
Patient self-perceived recovery and satisfaction			X***	X	X	X	X	X	X	X	X
Short Form 36 (SF36)	X			X	X	X	X	X	X	X	X
Physical examination	X					X	X			X	
Revisit and complications	With occurrence										

* 6 weeks visit may be performed also by the research nurse depending on the normal protocol hospital.

** Discharge form will be filled in depending on discharge moment.

*** Only self-perceived recovery is measured not self-perceived satisfaction.

Table 2. Non-inferiority margins

Outcome measurements	Expected differences	Non-inferiority margin
VAS leg pain (0-100 scale)	<5 **	5
ODI (0-100 scale)	<5 *	5
VAS low back pain (0-100 scale)	<5 *	5
SF36 (0-100)	<5*	5
Self-perceived recovery (% 1 and 2 on the 7-point Likert-scale)	<10%***	5
Patient satisfaction (% 4 on the 4-point Likert-scale)	<5%	5
Patient satisfaction (% 1 and 2 on the 7-points Likert-scale)	<5%	5
Scar satisfaction (1-10 scale)	<1	0.5
Patellar reflex (% normal reflexes)	<5%	5
Achilles reflex (% normal reflexes)	<5%	5
Straight leg raising test (% negative tests)	<5%	5
Cross straight leg raising (% negative tests)	<5%	5
Finger floor distance (cm)	<5	5
Muscle strength quadriceps (% normal muscular strength)	5%	5
Sensibility dermatomes L1-S1 (% normal sensibility)	5%	5
EQ-5D-5L	<0.05****	0.05
Costs (healthcare perspective)	<$500,- ***	250
Costs (societal perspective)	<$1500,- ***	500

* Obtained from the literature [13, 30]
** Obtained from the literature [13]
*** Obtained from the literature [30]
**** Obtained from the literature [31]

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

Section/item	Item No	Description	Addressed on page number
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	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____2 _____
Protocol version	3	Date and version identifier	_____4_____
Funding	4	Sources and types of financial, material, and other support	_____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1 and 15 ___
	5b	Name and contact information for the trial sponsor	_____1_____
	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	_____15 _____
	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)	____13 en 15____

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	____2 and 3____
	6b	Explanation for choice of comparators	____2 and 3____
Objectives	7	Specific objectives or hypotheses	_____3_____
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)	_____3 and 4 (see also design section)___
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	_____4_____
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)	_____4_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____5 and 6____
	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)	_____6 en 9_____
	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	_____6_____
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	_____6-8_____

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)	8
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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	5
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	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	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	6-11

	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	_____6_____
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	_____9_____
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	_____9-12_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__10 and 12____
	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)	_____9-10____
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	_ 9, 12, 15 and 16__
	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	_____9_____
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	__9,12 and 16___
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____12____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____12 and 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)	_____4_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____4_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____N.A._____
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	_____9____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____15 en 16____
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	__15 and 6_____
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	_____12_____
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	____12____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___15 __
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n.a._____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	appendix of bmj open online submission system__

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.

BMJ Open

The PTED study: design of a non-inferiority, randomised controlled trial to compare the effectiveness and cost-effectiveness of percutaneous transforaminal endoscopic discectomy (PTED) vs. open microdiscectomy for patients with a symptomatic lumbar disc herniation.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018230.R1
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Date Submitted by the Author:	20-Sep-2017
Complete List of Authors:	Seiger, Ankie; Vrije Universiteit Amsterdam, Health Sciences Gadjradj, Pravesh; Erasmusmc, Neurosurgery Harhangi, Sanjay; Erasmus MC, Neurosurgery van Susante, Job; Ziekenhuis Rijnstate, Orthopedics Peul, Wilco; Leiden University Medical Center, Neurosurgery Tulder, Maurits; University of Amsterdam, Health Sciences De Boer, Michiel; Vrije Universiteit Amsterdam, Health sciences Rubinstein, Sidney; Vrije Universiteit Amsterdam, Health Science
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Health economics, Epidemiology, Neurology
Keywords:	HEALTH ECONOMICS, NEUROSURGERY, ORTHOPAEDIC & TRAUMA SURGERY

The PTED study: design of a non-inferiority, randomised controlled trial to compare the effectiveness and cost-effectiveness of percutaneous transforaminal endoscopic discectomy (PTED) vs. open microdiscectomy for patients with a symptomatic lumbar disc herniation.

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Keywords: Surgery, lumbar disc herniation, open microdiscectomy, percutaneous transforaminal endoscopic discectomy, effectiveness, economic evaluation.

ABSTRACT

INTRODUCTION: Lumbosacral radicular syndrome is often caused by a disc herniation. The standard surgical technique to remove a disc herniation is open microdiscectomy. An alternative technique is Percutaneous Transforaminal Endoscopic Discectomy (PTED), which is less invasive. In The Netherlands, PTED is not currently considered standard care and therefore, not reimbursed within public health insurance. A pragmatic, multi-centre, non-inferiority, randomised controlled trial has been designed to determine the effectiveness and cost-effectiveness of PTED versus open microdiscectomy for the treatment of a lumbar disc herniation.

METHOD AND ANALYSIS: In total, 682 patients between 18-70 years of age with > 10 weeks of radiating pain or with > 6 weeks of excessive radiating pain are to be recruited from participating centres. Patients must have an indication for surgery based upon an MRI demonstrating compression of the nerve root from a lumbar disc herniation. Patients are to be randomised to PTED or open microdiscectomy. The primary outcome is self-reported leg pain measured by the 0-100 mm Visual Analogue Scale. Secondary outcomes include self-reported health and functional status; back pain; self-perceived recovery; and a physical examination. Outcomes will be measured the day following surgery, at 2, 4, and 6 weeks, and at 3, 6, 9, 12 and 24 months. Physical examination will be performed at 6 weeks, and 3 and 12 months. An economic evaluation will be performed from a societal perspective and cost-questionnaires will be used (e.g. EQ-5D-5L). The data will be analysed longitudinally; the non-inferiority margin for the primary outcome is 5. Bootstrapping techniques will be used for the economic evaluation.

ETHICS AND DISSEMINATION: This study has received approval of the Medical Ethical Committee of the VU Medical Centre Amsterdam: NL50951.029.14. The results will be published in an international peer reviewed scientific journal.

REGISTRATION: This trial is registered at ClinicalTrials.gov: NCT02602093.

Strengths and Limitations

- Large, multi-centre, pragmatic, randomised controlled trial
- Use of standardized and validated outcomes instruments
- Longitudinal and multi-level analysis
- Inclusion of an economic evaluation
- Potential performance bias due to the lack of blinding of patients and care providers

INTRODUCTION

Lumbosacral radicular syndrome is a common health problem with a lifetime prevalence that varies from 12.2% to 43% and has a point prevalence ranging from 1.6% to 13.4%.[1-6] Lumbosacral radicular syndrome is often caused by a lumbar herniated disc[7] and is associated with a greater incidence of sickness benefit,[8] increased pain and disability, and poorer quality of life[9] than those with non-specific low-back pain. In cases of a disc herniation, lumbosacral radicular syndrome can be treated either conservatively or surgically.[7]

To remove the disc herniation, the standard surgical technique is open microdiscectomy. A more recently developed technique is percutaneous transforaminal endoscopic discectomy (PTED). In short, open microdiscectomy is performed under general anaesthesia and surgeons operate with a direct vision on the herniated disc, while PTED is conducted transforaminally. These patients undergo local anaesthesia and surgeons operate through a working cannula with an indirect vision via an endoscope. Based upon the current

literature, PTED is a safe method for the removal of a lumbar disc herniation.[10] Possible benefits of PTED versus open microdiscectomy are: 1) Decreased medical costs because patients are treated on an outpatient basis; 2) It is easier to remove intra- and extra-foraminal herniated discs; 3) There is less chance of scar formation; and 4) The technique is potentially more effective for obese patients. However, too few, large prospective studies have examined this in detail, therefore, the benefits may be speculated.[11-13]

Despite that PTED is becoming more commonly used, there are still questions regarding its effect and the associated costs.[11, 13, 14] A recent systematic review[11] identified three randomised controlled trials (RCTs), which examined the effect of PTED compared to open microdiscectomy.[15-17] Their results suggest that there is low to very low quality evidence that PTED is not more effective than open microdiscectomy for self-reported back pain, leg pain, functional status, recovery, return-to-work, and satisfaction with surgery. Importantly, all three studies were of poor methodological quality and examined relatively few patients (i.e. ranging from 40 to 60 individuals). A more recent study concluded that PTED shows similar results compared to open microdiscectomy.[13] However, this was a single-centre study; it was conducted by a surgeon with a keen interest in the results of PTED; it included patients over a long period of time (i.e. the study started in 2006 and was published in 2017) suggesting possible selection of patients included in the trial; and the inclusion criteria published in the original protocol were different from those in the final publication. Additionally, the economic evaluation of this study has not yet been published.[18] This makes it difficult to assess the cost-effectiveness. Therefore, discussion regarding the effectiveness and cost-effectiveness of PTED remains.

In The Netherlands, the effectiveness of PTED has been heatedly debated. According to the Dutch Health Care Institute, a new surgical technique must meet certain requirements in order to be reimbursed by the public health insurance system. The Health Care Institute promotes the quality of Dutch Health Care and advises the Ministry of Health, Welfare and Sport on the content of the public health insurance. Based on a review,[11] the Health Care Institute claimed there is insufficient evidence for PTED to be included for reimbursement from the public health insurance package and as a result, patients are forced to pay the costs of the PTED treatment out-of-pocket. In 2017, the PTED and open microdiscectomy costs are approximately €5000 and €3000, respectively. In order to deal with this issue and to answer the remaining questions about PTED, this large, pragmatic, methodologically rigorous multi-centre study has been designed. The costs of PTED and open microdiscectomy will be fully reimbursed by the Dutch health insurance companies for patients participating in this study.

This study is expected to have a major societal impact because it will determine if PTED should be included in the Dutch health insurance package. Furthermore, this study will provide more insight in PTED internationally, resulting in improved care for patients with a lumbar disc herniation. The primary hypothesis of this study is that PTED is not less effective and not less cost-effective compared to standard care (i.e. open microdiscectomy) for patients with symptomatic, lumbosacral radicular syndrome as a result of a lumbar disc herniation. Therefore, a non-inferiority design will be used.

METHOD AND ANALYSIS

Study design

A pragmatic, multi-centre non-inferiority randomised controlled trial (RCT) will be used. Following the baseline measurements, wherein clinical and socio-demographic measurements will be collected, patients are to be randomised to one of the two groups: the control group will receive standard open microdiscectomy and the intervention group will receive PTED. Patients will be followed for two years, but the primary analysis will be conducted on the one-year data.

Important protocol modifications will be registered at ClinicalTrials.gov and communicated to all relevant parties involved in this study (Medical Ethical Committee, ZonMw, included patients, participating surgeons, and members from the advisory board (listed in the acknowledgments)).

Study population

In total, 682 patients with a magnetic resonance imaging (MRI) confirmed lumbosacral radicular syndrome, due to a lumbar disc herniation are to be recruited. Patients will be recruited from five hospitals and one private health clinic located in Arnhem/Zevenaar, Leiderdorp, Tilburg and Rotterdam (The Netherlands). Each patient is required to sign a written informed consent prior to participation.

In order to be eligible to participate and in accordance with the Dutch Guideline Lumbosacral Radicular Syndrome,[19] a subject must meet all of the following conditions:

Inclusion criteria

- 18-70 years of age;
- > 10 weeks of radiating pain with or without motor or sensory loss in the leg, or with > 6 weeks of excessive radiating pain and no tendency for any clinical improvement;
- Indication for surgery;
- MRI demonstrating a lumbar disc herniation with nerve compression with or without concomitant spinal or lateral recess stenosis or sequestration;
- Sufficient knowledge of the Dutch language in order to complete forms and follow instructions independently.

Exclusion criteria

- Previous surgery on the same or adjacent disc level;
- Cauda equina syndrome;
- Spondylytic- or degenerative spondylolisthesis;
- Pregnancy;
- Severe comorbid medical or psychiatric disorder (American Society of Anaesthesiologists >2);
- Severe caudal or cranial sequestration;
- Contra-indication for surgery;
- Moving abroad at short notice.

Study procedures

Participating surgeons will screen all eligible patients with a lumbar disc herniation during the consultation (Table 1). If eligible for inclusion, patients will receive information relevant to the study by means of a letter. Dutch law requires that patients are given at least two days to consider participation. Following this initial screening, the patient is to be examined by a trained research nurse and the informed consent is obtained; baseline measurements will be performed; and patients will be randomised.

Randomisation

Patients will be randomised in a 1:1 ratio to PTED or open microdiscectomy. An experienced statistician will prepare computer-generated, random number tables. Treatment allocation will be concealed. The key will be withheld from all participants and researchers involved in this study. Variable block sizes of 4, 6 and 8 will be used and stratified by treatment centre. The random-number tables will be entered into a computer system by an independent software company, and allocation will be performed by the computer system once baseline data and physical examination are to be obtained from an independent research nurse responsible for the treatment allocation.

Blinding

No attempt will be made to blind the patients. Blinding is considered impossible, because the procedures are fundamentally different. Furthermore, outcomes assessors cannot be blinded, given that the primary outcomes are all self-reported. The analysis will be performed blinded for treatment allocation.

Treatment

Intervention: Percutaneous Transforaminal Endoscopic Discectomy (PTED)

PTED is to be conducted as follows:[20] local anaesthesia is to be administered and consists of light sedation with dexmedetomidine or a combination of propofol and remifentanil for the convenience of the patient. The amount of administered sedation should still allow the patient to respond to nerve root manipulation. Verification of the site is to be performed by an image intensifier using fluoroscopy (anteroposterior and lateral view) and is depending upon the patient's posture. An incision just above the dorsolateral side of the pelvis is conducted, where a needle is to be set from the incision to the superior articular process of the lower involved vertebrae of the herniated disc. Position will be checked again under fluoroscopy. After the needle has reached the superior articular process, a guide wire is to be inserted. Following that, a series of conical rods are to be introduced, subsequently a drill/reamer is to be introduced through the cannula and rods. After drilling through the superior articular process is conducted in order to enlarge the neuroforamen, the instruments are to be removed, but the guidewire is left in place and the endoscope with the working channels are to be introduced via an 8 mm cannula. The image intensifier ensures that the position of the cannula is maintained. Following removal of the disc herniation with a rongeur, the cannula and endoscope are removed. The patient is to be treated on an outpatient basis. In order to decompress the nerve root, it is sometimes necessary to remove the superior articular process. With the outside-in technique this can be successfully performed.[10, 20]

Comparison: Open microdiscectomy

Open microdiscectomy is to be conducted as follows: general or spinal anaesthesia is to be administered. Verification is to be performed using a fluoroscopy and the patient is to be positioned prone or in the salaam position. Loupe or microscope magnification may be used according to the surgeon`s preference. A paramedian

incision is to be performed and the level is to be indicated. Following the identification of the lamina, the yellow ligament will be removed to identify the nerve root and disc herniation. Laminotomy as well as foraminotomy is to be performed, if necessary. For the foraminal herniated disc we will use a partial medial facetectomy and for the
extra-foraminal herniated disc a parafacetal approach. For all surgeries, the amount of degenerative disc material shall be removed at the discretion of the attending surgeon. Post-operative policy will be followed and it is expected that the duration of recovery in the hospital may vary from 1-2 days, but the patient will be discharged as soon as medically responsible.

Co-interventions

Pain medication will be offered to patients, should this be necessary. In addition, use of co-interventions will be monitored by self-reported cost questionnaires, in which medication usage and any health care utilization is recorded throughout the follow-up period.

Learning curve

It will be necessary to train surgeons in the use of PTED. Prior to the start of this study only two surgeons in The Netherlands were proficient in this technique. One of these surgeons is participating in this study (BSH). This experienced surgeon will provide the training to the other surgeons, all of whom have more than ten years of surgical experience. The initial training will be first conducted on cadavers, and only once the surgeons are comfortable with the use of the procedure, they will then perform this technique on patients under the tutelage of the PTED-experienced surgeon. It is expected that 50 patients per surgeon will be necessary to become proficient in PTED (defined as the 'learning curve'). Thus, 150 PTED patients will be registered as learning curve patients. Additionally, competency in the use of PTED by the surgeons is to be evaluated using skill-based questions measured by a Likert-scale and the Objective Structured Assessment of Technical Skills (OSATS). These will be recorded and evaluated by both the teaching surgeon as well as the surgeons undergoing the training.[21]

Prognostic factors

The following potential prognostic factors are to be measured: 1) socio-demographic characteristics (e.g. age, gender); 2) characteristics of the complaint (e.g. duration and severity); 3) baseline pain and functional disability; 4) lifestyle factors (e.g. smoking and alcohol use); 5) psychological factors (e.g. expectations of recovery, emotional well-being; 6) psychopathology as measured with the four dimensional symptom questionnaire (4DSQ; dimensions: distress, depression, anxiety and somatization);[22] 7) work-related factors (e.g. physical workload, job satisfaction); and 8) previously received treatment due to the same episode of back complaints (e.g. medication and physiotherapy).

Outcome measurements

The outcomes are to be measured by validated self-reported questionnaires and by physical examination. Data are to be collected prior to randomisation (baseline), the day following surgery, at 2, 4, and 6 weeks, and at 3, 6, 9, 12, and 24 months following surgery (Table 1).
All questionnaires will be sent automatically by e-mail with a personal link to the digital questionnaire. If necessary, a reminder will be sent after 3 days; after six days the research nurse will call the patient with the request to fill in the questionnaire. Deviations from the protocol (e.g. conversion from PTED to open microdiscectomy) will be registered and outcomes will continue to be measured.

Primary outcomes

The primary outcome, leg pain, is to be measured by the Visual Analogue Scale (VAS; scale 0-100 mm). This outcome measure has been identified in a systematic review to be one of the most commonly measured outcomes, and is specific and responsive to change in a population undergoing lumbar spine surgery.[23]

Secondary outcomes

Functional status: will be measured with the Oswestry Disability Index (ODI). The ODI[24] is one of the principal condition-specific outcome measures used in the management of spinal disorders. The ODI (2.1a) is to be used.[25] The ODI has been extensively tested and showed good psychometric properties.[26]

Low-back pain: will be measured with the VAS (scale ranging from 0mm (no pain) to 100mm (worst imaginable pain)).

Generic quality of life: will be measured with the Dutch version of the short form SF36. The SF-36 questionnaire has been validated and found reliable for low back pain.[27] The questions are divided into eight domains: 1) physical functioning, 2) physical role limitations, 3) emotional role limitations, 4) social functioning, 5) physical pain, 6) general mental health, 7) vitality, and 8) general health perception. Per domain the scores of the items are added up and transformed into a scale of 0 to 100. A higher score reflects a better health condition. In addition, these eight domains can be summarized in a physical and psychological main domain.

Self-perceived recovery of the patient: will be measured with a seven-point Likert-scale. The score on this scale varies from 'completely recovered' to 'worse than ever'. We will dichotomize the outcome with 'completely recovered', 'moderately recovered' and 'a bit recovered' as 'recovered' and the other four categories as 'not recovered'.

Patient satisfaction: will be measured using the Likert-scale, Body Image and the Cosmesis scale.[28, 29] Body satisfaction will be measured using a four-point Likert-scale (ranging from 'not at all', 'a little', 'quite', to 'yes, very much'). Satisfaction change of complaints and satisfaction treatment will be measured using a seven-point Likert-scale (ranging from 'completely satisfied with current symptoms' to 'completely dissatisfied with current symptoms'). The scales will be completed by the patients prior to and following surgery. Scar satisfaction will also be measured using the seven-point Likert-scale and with a 1-10 numeric rating scale (ranging from 1 = 'as ugly as conceivable' to 10 = 'almost no scar perceived').

Physical examination: will be performed at 6 weeks, and at 3 and 12 months following surgery. This will include: scar size; patellar and Achilles tendon reflexes; straight leg raising test; cross straight leg raising test; finger-floor distance; strength measurement of the quadriceps using the Medical Research Council (MRC); sensibility dermatomes L1-S1, abdominal muscle strength; and patients' weight. The patellar and tendon reflexes are to be measured in a sitting upright position with both feet dangling above the ground. Tendon reflexes are tapped up to a maximum of two times with the reflex hammer. Reflexes are distinguished into absent, reduced, normal, increased, and clonus reflexes. The straight leg raising test and cross straight leg raising test are both measured as negative when no shooting leg pain is perceived, and positive when shooting pain is perceived. Finger-floor

distance is the distance between the longest finger and the floor when the patients perform a forward bent with the knees extended. Muscle strength of the quadriceps is measured from a sitting position. Patients will be asked to extent their knee while the research nurse exerts counter-pressure just above the ankle. Muscle strengths are rated on the Dutch version of the MRC, ranging from 0= no contraction to 5 = normal muscle strength. For the sensibility the research nurse checks every dermatome area (L1-S1) by touching the patient with a sharp and blunt object. Patients indicate with their eyes closed when sensation is felt. Sensibility varies from decreased, normal or increased sensibility compared to the other leg. Abdominal strength is measured by counting the maximal number of abdominal crunches from the supine position. Patients are asked to reach the hands towards the bended knees and to lift the scapulae from the surface. At any time, the lumbar spine will be supported by the underlying surface to minimalize the range of motion of the lumbar spine. Without an increase of pain the maximum is set at a cut-off point of 26 crunches.

Screening and operation case record forms are to be completed by the surgeons, while discharge forms, physical examination and baseline intake forms are to be completed by a trained research nurse.

Table 1. Flowchart visits and case report forms

Visits and Case report forms	Intake + baseline	Surgery	1-2 days following treatment	2 weeks following treatment	4 weeks following treatment	6 weeks following treatment	3 months following treatment	6 months following treatment	9 months following treatment	12 months following treatment	24 months following treatment
Surgeon visit	X					X*					
Informed consent	X										
Research nurse visit	X					X	X			X	
Randomisation	X										
Surgery		X									
Discharge		X**	X**								
Four-Dimensional Symptom Questionnaire (4DSQ)	X										
Oswestry Disability Index (ODI)	X		X	X	X	X	X	X	X	X	X
Cost questionnaires	X			X	X	X	X	X	X	X	
EuroQol (EQ-5D-5L)	X		X	X	X	X	X	X	X	X	X
VAS leg pain, VAS Back pain	X		X	X	X	X	X	X	X	X	X
Quality of Life VAS	X		X	X	X	X	X	X	X	X	X
Patient self-perceived recovery and satisfaction			X***	X	X	X	X	X	X	X	X
Short Form 36 (SF36)	X			X	X	X	X	X	X	X	X
Physical examination	X					X	X			X	
Revisit and complications	With occurrence										

* 6 weeks visit may be performed also by the research nurse depending on the normal protocol hospital.

** Discharge form will be filled in depending on discharge moment.

*** Only self-perceived recovery is measured not self-perceived satisfaction.

Complications, operative morbidity, and re-operations

Immediately following surgery and discharge, the surgeon and research nurse will perform a systematic assessment of complications (including urinary tract infection, secondary bleeding, and progressive neurological deficit). In addition, surgeons will record any perioperative complications like cerebrospinal fluid leakage, nerve root damage, and if the surgery was initiated at the wrong disc level. Re-operation at the initial site is to be considered a poor outcome. Re-operation in both groups will be recorded. Perioperative morbidity will be assessed with operation time, perioperative blood loss, hospital stay and re-operative rate as related to the primary condition (lumbar disc herniation).

Sample size calculation

The mean difference and standard deviation (SD) for the VAS (leg pain) used in the sample size calculation was: mean 5; SD 14.9.[30] The margin of non-inferiority was set at 5, (one-sided) alpha at 0.05 and beta at 0.10 (power 0.9). We estimated that in total 306 patients are needed to demonstrate non-inferiority on the primary outcome. Accounting for 20% attrition, the aim is to recruit 382 patients. As the Ministry of Health in the Netherlands has stipulated that PTED will only be reimbursed if patients participate in the randomised trial, an extra 300 patients will be necessary for the inclusion of 150 patients in the PTED learning curve. Consequently, a total of 682 patients will be recruited for this study. Patients are likely to participate in this study, because PTED will only be reimbursed by Dutch health care insurance for participants in this study. Therefore, reaching the target sample size is not likely to become a problem.

Data analysis

Data analysis will be conducted by a researcher or statistician blinded for treatment allocation after follow-up is finished. No interim analysis will be performed.

All data handling (entry, coding, storage and analysis) is confidential and complies with the Dutch Personal Data Protection Act. The anonymous data are stored in a central warehouse for at least 15 years.

Effect analysis

Characteristics of the patients will be presented using descriptive statistics (mean (SD), median (range) or proportion) to assess if balanced groups were obtained after randomisation. The non-inferiority margins are set and listed in table 2.

Table 2. Non-inferiority margins

Outcome measurements	Expected differences	Non-inferiority margin
VAS leg pain (0-100 scale)	<5 **	5
ODI (0-100 scale)	<5 *	5
VAS low back pain (0-100 scale)	<5 *	5
SF36 (0-100)	<5*	5
Self-perceived recovery (% 1 and 2 on the 7-point Likert-scale)	<10%***	5
Patient satisfaction (% 4 on the 4-point Likert-scale)	<5%	5
Patient satisfaction (% 1 and 2 on the 7-points Likert-scale)	<5%	5
Scar satisfaction (1-10 scale)	<1	0.5
Patellar reflex (% normal reflexes)	<5%	5
Achilles reflex (% normal reflexes)	<5%	5
Straight leg raising test (% negative tests)	<5%	5
Cross straight leg raising (% negative tests)	<5%	5
Finger floor distance (cm)	<5	5
Muscle strength quadriceps (% normal muscular strength)	5%	5
Sensibility dermatomes L1-S1 (% normal sensibility)	5%	5
EQ-5D-5L	<0.05****	0.05
Costs (healthcare perspective)	<$500,- ***	250
Costs (societal perspective)	<$1500,- ***	500

* Obtained from the literature [13, 30]
** Obtained from the literature [13]
*** Obtained from the literature [30]
**** Obtained from the literature [31]

The primary data analysis will examine the effects of PTED for leg pain for those patients not in the learning curve, and shall be conducted according to the intention-to-treat principle. If necessary, missing items will be imputed using multiple imputation techniques. Linear and generalized multi-level analyses will be used, accounting for dependency of measurements over time within patients and patients nested within the surgeons, representing a 3-level model: time, patient and surgeon. The data are to be examined longitudinally and the primary analysis will be aimed at average differences in effectiveness between the two treatment modalities. We will also include treatment * time interactions to explore whether these effects are different over time. In addition to the crude analyses, all analyses will be adjusted for potential confounders, such as age, gender, nature and severity of the presenting complaint. In a secondary analysis, a per-protocol analysis shall be conducted. The secondary continuous outcomes, such as low-back pain, functional status, will be analysed similar to the primary data analysis; however, recovery and some of the physical performance measures (Table 2) are to be treated as a dichotomous variable and will be analysed in logistic regression analyses.

Complications will be summarized for the time period of the study, but also presented for those complications encountered before and after 6 weeks.

Subgroup analyses effect

Subgroup analysis will be conducted in those patients with a) paramedian/median disc herniation b) foraminal/extra-foraminal disc herniation, and c) L5-S1 disc herniation. The goal of the subgroup analyses is to test the robustness of the data to changes in underlying assumptions regarding the type or location of the

hernia. In addition, we will examine the effects for all patients, including those in the 'learning curve' in order to determine if these outcomes are different than the primary analyses.

Results from all analyses will be expressed as mean effect estimate with 95% confidence intervals and these estimates will be subsequently compared to the margin of non-inferiority in order to make inferences about the non-inferiority of the intervention, PTED.

Economic evaluation

Both cost-effectiveness and cost-utility analysis will be conducted from a societal perspective alongside the RCT. We will measure, value, and analyse total costs of all patients and relate the difference in costs to the difference in effects between the two groups.

Direct costs include costs of the interventions, hospitalisation after surgery, medication and other health care utilization. Patient costs and cost of productivity loss, absenteeism and presenteeism, will also be included. Health care utilization, patients cost and productivity loss will be measured using self-completed cost questionnaires. The cost of the interventions will be estimated using a bottom-up approach (micro-costing) and hospitalisation will be registered using case record forms. The Dutch tariff of the EQ-5D-5L will be used to calculate the quality-adjusted life years (QALYs).[32, 33] The EuroQol measures the five dimensions: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. Each dimension consists of one item, while five levels are distinguished ('no', 'slight', 'moderate', 'severe problems', 'unable to do').

Costs resulting from productivity loss are to be estimated using the friction cost method, which assumes that sick workers are replaced after a period of time (i.e. 12 weeks).[34] Mean productivity costs per working hour are to be adjusted for age and gender and used to estimate the cost of absenteeism. Health care utilization is to be valued according to the guidelines published in the updated handbook for economic evaluation in The Netherlands.[34] Medication is to be valued using prices from the Royal Dutch Society for Pharmacy.[35]

Cost-effectiveness analysis

Total costs will be related to the primary effect measure, leg pain. A cost-utility analysis will be performed with QALYs. From the EQ-5D-5L utilities will be obtained and QALYs will be calculated using linear interpolation between measurement points. The primary analysis will be conducted according to intention-to-treat. Missing data will be imputed using multiple imputation by changed equations.[36] Incremental Cost Effectiveness Ratios (ICERs) will be calculated by dividing the difference in costs by the difference in effects. We will perform a cost-effectiveness analysis with leg pain and a cost-utility analysis with QALYs as outcome. In order to account for the possible clustering of data, analyses will be performed using linear multilevel analyses.[37] Bias corrected and accelerated bootstrapping with 5,000 replications will be performed in order to estimate 95% confidence intervals around cost differences and the uncertainty surrounding the ICERs. Uncertainty will be shown in cost-effectiveness planes and cost-effectiveness acceptability curves, and sensitivity analyses will be performed to test the robustness of the study results.[38-40]

Sensitivity analysis cost-effectiveness

Sensitivity analyses will be conducted for the most important cost drivers in order to determine the robustness of the findings. In addition, the main analyses are to be repeated using only complete cases (i.e. complete clinical outcome data and complete cost data). Lastly, the impact of the Human Capital Approach will be compared to the friction cost method approach. The Human Capital Approach evaluates the total costs of productivity loss without considering the possibility of replacing the sick worker.

ETHICS AND DISSEMINATION

This study has received approval of the Medical Ethical Committee of the VU Medical Centre Amsterdam and confirmation can be supplied upon request [corresponding number: NL50951.029.14; November 5, 2015]. Serious adverse events (SAE) and adverse events will be registered; SAE will be reported within 24 hours (see section 'complications, operative morbidity, and re-operations'). The sponsor has an insurance, which is in accordance with the legal requirements in the Netherlands. The insurance applies to the damage that becomes apparent during the study or within four years after the end of the study. This study will be monitored according to a detailed monitoring plan adapted to the risk classification of the Dutch University Federation guidelines. Based on this guideline, the risk classification of this study is regarded negligible. Considerations in this assessment are that this is an investigator-initiated trial, not with vulnerable patients, and while side effects are known, such as nerve root damage, severe adverse events are extremely rare. Audits may be required by and will be granted to the Medical Ethical Committee and to the regulatory authority inspections. Patients' permission for these audits is obtained with informed consent.

The final trial results will be communicated to participants, healthcare professionals, professional organisations and relevant guideline committees in the Netherlands. We will publish the results in an international peer reviewed open access scientific journal. There are no publication restrictions.

DISCUSSION

This large, multi-centre, pragmatic study will be conducted to resolve the discussion regarding the effects and costs of PTED compared to open microdiscectomy for patients with a lumbosacral radicular syndrome caused by a lumbar disc herniation. Learning curve patients and foraminal/extraforaminal disc herniations will be included, because the Dutch Ministry of Health and the Netherlands Organisation for Health and Research Development (ZonMw) requested this. At the moment, in the Netherlands PTED does not comply with standards of practice and is not included in the Dutch public healthcare package. However, The Dutch Ministry of Health classified PTED as an important technique to examine and decided that PTED will be conditionally admitted to the Dutch public health insurance package for those patients participating in this study. In other words, insurance companies are obliged to reimburse PTED for patients participating in this study. This conditional reimbursement only applies during the four years of this study. After this study a decision will be made if PTED should or should not be included in the Dutch public health insurance package. Open microdiscectomy is already included in the Dutch public health insurance package and reimbursed for all patients. This advantage of reimbursement presented a unique challenge, because this means that all patients are to be included from the beginning of this agreement. Thus, patients will be included also when surgeons are still undergoing the PTED training (learning curve patients). The other requirement was that the inclusion and exclusion criteria had to be in accordance with the Dutch Guideline Lumbosacral Radicular Syndrome and similar to an earlier study

performed in this field.[19, 41] For this reason, also patients with foraminal and extraforaminal disc herniations will be included in this study. Extra subgroup analysis will be performed in order to assess possible differences in effect. In order to prevent discussion regarding the effects of PTED following this study, a document was signed by all participating parties (e.g. professional surgical organisations, insurance companies, Dutch healthcare institute) to agree upon the study design and the criteria for in- or exclusion of PTED from the Dutch public health insurance package.

Since the trial was published in a trial registry (clinicaltrials.gov; November 2013), the protocol has been modified. A physical examination has been added in order to obtain more objective information regarding the physical rehabilitation and a numeric rating scale (NRS) has been added in order to measure back, leg pain and quality of life. The reason for the latter is, the VAS may be completed by participants using different digital apparatuses (i.e. PC, tablet or mobile phone), with the result that the lengths of the VAS scale may vary. The validity and reliability is, therefore, uncertain. Based upon the literature, it would appear that the NRS and VAS demonstrate comparable values for pain following surgery;[42] however, the aforementioned issue, namely the use of the VAS on different digital apparatuses has not previously been examined. In order to determine whether this has bearing on the outcomes, a sensitivity analysis shall be conducted, and we will examine the correlation between the VAS and NRS.

The trial is an ongoing study and runs from February 2016 to February 2020.

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FOOTNOTES

Contributorship statement:

SH, JvS, WP, MvT, SR contributed to writing the proposal and acquiring the grant from The Netherlands Organisation for Health and Care Research (ZonMw). AS prepared the first draft of the study protocol. All authors (AS, PG, SH, JvS, WP, MvT, MdB, SR) contributed to the final design of this study protocol, assisted with drafting the manuscript, and approved the final version of the manuscript. MdB developed the statistical analysis plan.

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Competing interest statement:
The professional judgment concerning the primary interest (e.g. validity of the research) will not be influenced by a secondary interest. All authors have read and understood the BMJ policy on declaration of interests. We all declare that we have no competing interests other than receiving grants. For this particular study we had financial support from The Netherlands Organisation for Health Research and Development. We do not have relationships with any organisations that might have an interest in the submitted work. All authors have completed the ICJE uniform at www.icmje.org/coi_disclosure.pdf.

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Data sharing statement:
This article refers to a study protocol; data are not yet available. We will share all data through open access once the final results have been published.

Ethical approval: This study has received approval of the Medical Ethical Committee of the VU Medical Centre Amsterdam and confirmation can be supplied upon request [corresponding number: NL50951.029.14; November 5, 2015].

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

Section/item	Item No	Description	Addressed on page number
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	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____2 _____
Protocol version	3	Date and version identifier	_____4_____
Funding	4	Sources and types of financial, material, and other support	_____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1 and 15 ___
	5b	Name and contact information for the trial sponsor	_____1_____
	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	_____15 _____
	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)	____13 en 15____

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	____2 and 3____
	6b	Explanation for choice of comparators	____2 and 3____
Objectives	7	Specific objectives or hypotheses	_____3_____
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)	_____3 and 4 (see also design section)___
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	_____4_____
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)	_____4_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____5 and 6____
	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)	_____6 en 9_____
	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	_____6_____
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	_____6-8_____

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)	8
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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
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	5
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	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	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	6-11

	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	_____6_____
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	_____9_____
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	_____9-12_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__10 and 12____
	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)	_____9-10____
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	_ 9, 12, 15 and 16__
	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	_____9_____
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	__9,12 and 16___
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____12____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____12 and 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)	_____4_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____4_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____N.A._____
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	_____9____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____15 en 16____
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	__15 and 6_____
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	_____12_____
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	____12____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___15 __
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n.a._____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	appendix of bmj open online submission system__

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.