BMJ Open

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

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To cite: Seiger A, Gadjradj PS, Harhangi BS, *et al*. PTED study: design of a non-inferiority, randomised controlled trial to compare the effectiveness and cost-effectiveness of percutaneous transforaminal endoscopic discectomy (PTED) versus open microdiscectomy for patients with a symptomatic lumbar disc herniation. *BMJ Open* 2017;**7**:e018230. doi:10.1136/bmjopen-2017-018230

► Prepublication history for this paper is available online. To view please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-018230).

Received 21 June 2017
Revised 20 September 2017
Accepted 27 September 2017

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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 as standard care, and therefore not reimbursed within public health insurance. A pragmatic, multicentre, non-inferiority, randomised controlled trial has been designed to determine the effectiveness and cost-effectiveness of PTED versus open microdiscectomy for the treatment of lumbar disc herniation.

Method and analysis In total, 682 patients between 18 and 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 on 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 (eg, 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.

Strengths and limitations of this study

- Large, multicentre, pragmatic, randomised controlled trial.
- Use of standardised and validated outcomes instruments.
- Longitudinal and multilevel analysis.
- Inclusion of an economic evaluation.
- Potential performance bias due to the lack of blinding of patients and care providers.

Trial registration number NCT02602093; Pre-results, recruiting stage.

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 on 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 the following: (1) decreased medical costs because patients are treated on an outpatient basis; (2) it is easier to remove intraforaminal and extraforaminal 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 and 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) that examined the effect of PTED compared with open microdiscectomy.[15–17] Their results suggest that there is low-quality 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 (ie, ranging from 40 to 60 individuals). A more recent study concluded that PTED shows similar results compared with 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 (ie, 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 healthcare 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 that 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 multicentre 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 with standard care (ie, open microdiscectomy) for patients with symptomatic, lumbosacral radicular syndrome as a result of lumbar disc herniation. Therefore, a non-inferiority design will be used.

METHOD AND ANALYSIS

Study design

A pragmatic, multicentre, non-inferiority RCT will be used. Following the baseline measurements, wherein clinical and sociodemographic 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 2 years, but the primary analysis will be conducted on the first year's 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 acknowledgements)).

Study population

In total, 682 patients with an 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 on lumbosacral radicular syndrome,[19] a subject must meet all of the following criteria.

Inclusion criteria

- Aged 18–70 years;
- More than 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 Anesthesiologists >2),
- Severe caudal or cranial sequestration,
- Contraindication for surgery,
- Moving abroad at short notice.

Study procedures

Participating surgeons will screen all eligible patients with 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 2 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 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: 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 on the patient's posture. An incision is made just above the dorsolateral side of the pelvis, 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 guidewire 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 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 to be 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 extraforaminal herniated disc, we will use a parafacetal approach. For all surgeries, the amount of degenerative disc material shall be removed at the discretion of the attending surgeon. Postoperative policy will be followed, and it is expected that the duration of recovery in the hospital may vary from 1 to 2 days, but the patient will be discharged as soon as medically responsible.

Cointerventions

Pain medication will be offered to patients, should this be necessary. In addition, use of cointerventions will be monitored by self-reported cost questionnaires, in which medication usage and any healthcare utilisation 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 10 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 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

Table 1 Flow chart 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					

*Six-week visit may be performed also by the research nurse depending on the normal protocol of the hospital.
†Discharge form will be filled in depending on discharge moment.
‡Only self-perceived recovery is measured, not self-perceived satisfaction.
VAS, visual analogue scale.

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. These will be recorded and evaluated by both the teaching surgeon and the surgeons undergoing the training.[21]

Prognostic factors

The following potential prognostic factors are to be measured: (1) sociodemographic characteristics (eg, age and gender), (2) characteristics of the complaint (eg, duration and severity), (3) baseline pain and functional disability, (4) lifestyle factors (eg, smoking and alcohol use), (5) psychological factors (eg, expectations of recovery and emotional well-being), (6) psychopathology as measured with the Four-Dimensional Symptom Questionnaire (4DSQ; dimensions: distress, depression, anxiety and somatisation),[22] (7) work-related factors (eg, physical workload and job satisfaction) and (8) previously received treatment due to the same episode of back complaints (eg, 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 email with a personal link to the digital questionnaire. If necessary, a reminder will be sent after 3 days; after 6 days, the research nurse will call the patient with the request to fill in the questionnaire. Deviations from the protocol (eg, 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 0 (no pain) to 100 mm (worst imaginable pain)).

Generic quality of life will be measured with the Dutch version of the Short Form 36 (SF36). The SF36 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 0–100. A higher score reflects a better health condition. In addition, these eight domains can be summarised 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 dichotomise 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' and '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 revolting 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; crossed 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 crossed 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 bend 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 counterpressure 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 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 with 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 bent knees and to lift the scapulae from the surface. At any time, the lumbar spine will be supported by the underlying surface to minimalise 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.

Complications, operative morbidity and reoperations

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. Reoperation at the initial site is to be considered a poor outcome. Reoperation in both groups will be recorded. Perioperative morbidity will be assessed with operation time, perioperative blood loss, hospital stay and reoperative rate as related to the primary condition (lumbar disc herniation).

Sample size calculation

The mean difference and 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 healthcare 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 are 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[13]	5
ODI (0–100 scale)	<5[13 30]	5
VAS low back pain (0–100 scale)	<5[13 30]	5
SF36 (0–100)	<5[13 30]	5
Self-perceived recovery (% 1 and 2 on the 7-point Likert scale)	<10[30]	5
Patient satisfaction (% 4 on the 4-point Likert scale)	<5	5
Patient satisfaction (% 1 and 2 on the 7-point 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
Crossed 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[42]	0.05
Costs (healthcare perspective)	<$500[30]	250
Costs (societal perspective)	<$1500[30]	500

ODI, Oswestry disability index; SF36, Short form 36; VAS, visual analogue scale.

The primary data analysis will examine the effects of PTED for leg pain for those patients who are 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 generalised multilevel analyses will be used, accounting for dependency of measurements over time within patients and patients nested within the surgeons, representing a three-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 and 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 summarised for the time period of the study and will be presented for those complications encountered before and after 6 weeks.

Subgroup analyses effect

Subgroup analysis will be conducted in those patients with (1) paramedian/median disc herniation, (2) foraminal/extraforaminal disc herniation and (3) 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 from the primary analyses.

Results from all analyses will be expressed as mean effect estimate with 95% CIs, and these estimates will be subsequently compared with 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 analyses 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 healthcare utilisation. Patient costs and cost of productivity loss, absenteeism and presenteeism will also be included. Healthcare utilisation, 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 (microcosting), 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).[31 32] 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' and '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 (ie, 12 weeks).[33] Mean productivity costs per working hour are to be adjusted for age and gender and used to estimate the cost of absenteeism. Healthcare utilisation is to be valued according to the guidelines published in the updated handbook for economic evaluation in the Netherlands.[33] Medication is to be valued using prices from the Royal Dutch Society for Pharmacy.[34]

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.[35] 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.[36] Bias corrected and accelerated bootstrapping with 5000 replications will be performed in order to estimate 95% CIs 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.[37–39]

Sensitivity analysis economic evaluation

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 (ie, complete clinical outcome data and complete cost data). Lastly, the impact of the human-capital approach will be compared with 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.

Dissemination

Serious adverse events (SAE) and adverse events will be registered; SAE will be reported within 24 hours (see Complications, operative morbidity and

reoperations section). 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 4 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 the Medical Ethical Committee or by the regulatory authority inspections and will be granted if neccessary. Patients' permission for these audits is obtained with informed consent.

The final trial results will be communicated to the 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, multicentre, pragmatic study will be conducted to resolve the discussion regarding the effects and costs of PTED compared with open microdiscectomy for patients with 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 4 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 40] 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 (eg, professional surgical organisations, insurance companies and Dutch Health Care Institute) to agree on the study design and the criteria for inclusion 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 and leg pain, and quality of life. The reason for the latter is that the VAS may be completed by participants using different digital apparatuses (ie, 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 on the literature, it would appear that the NRS and VAS demonstrate comparable values for pain following surgery;[41] however, the aforementioned issue, namely the use of the VAS on different digital apparatuses, has not been examined previously. In order to determine whether this has a 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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Acknowledgements Dr. P.R.A.M. Depauw, Dr P.J. Schutte, Dr A W.J. Vreeling, Dr C. L. A. M. Vleggeert-Lankamp, ; the hospitals, Albert Schweitzer Ziekenhuis, Alrijne Ziekenhuis, Elisabeth-Tweesteden Ziekenhuis, Franciscus Gasthuis en Vlietland, Park Medisch Centrum, Rijnstate Ziekenhuis; and the Advisory Committee: Dr J L P Kuijpens, Zorgverzekeraars Nederland, patient organisation 'Nederlandse Vereniging van Rugpatiënten de "Wervelkolom"', Dutch Spine Society, Nederlandse Orthopaedische Vereniging.

Contributors BSH, JLCvS, WCP, MWvT and SMR 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, PSG, BSH, JLCvS, WCP, MWvT, MRdB and SMR) contributed to the final design of this study protocol, assisted with drafting the manuscript and approved the final version of the manuscript. MRdB developed the statistical analysis plan.

Funding This study was funded by ZonMw, The Netherlands Organisation for Health Research and Development (project number 837004013).

Competing interests None declared.

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

Provenance and peer review Not commissioned; externally peer reviewed.

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