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Cost-effectiveness of Early Surgery versus Conservative Treatment with Optional Delayed Meniscectomy for Patients over 45 years with non-obstructive meniscal tears (ESCAPE study): protocol of a randomised controlled trial

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ABSTRACT

Introduction: Recent studies show similar outcome between surgery and conservative treatment in patients with non-obstructive meniscal tears. However, surgery is still often preferred over conservative treatment. When conservative treatment is non-inferior to surgery, shifting the current standard treatment choice to conservative treatment alone could save over €30 millions of direct medical costs on an annual basis. Economic evaluation studies comparing surgery to conservative treatment are lacking.

Methods and analysis: A multicentre randomised controlled trial (RCT) with an economic evaluation alongside was performed to assess the (cost)-effectiveness of surgery and conservative treatment for meniscal tears. We will include 402 participants between 45 and 70 years with an MRI-confirmed symptomatic, non-obstructive meniscal tears to prove non-inferiority of conservative treatment. Block randomisation will be web-based. The primary outcome measure is a physical function, measured by the International Knee Documentation Committee 'Subjective Knee Form'. Furthermore, we will perform a cost-effectiveness and cost-utility analysis from societal perspective and a budget impact analysis from a societal, government and insurer perspective. Secondary outcomes include general health, quality of life, activity level, knee pain, physical examination, progression of osteoarthritis and the occurrence of adverse events.

Ethics and dissemination: This RCT will be performed in accordance with the Declaration of Helsinki and has been approved by the Ethics Committee (number NL44188.100.13). The results of this study will be reported in peer-reviewed journals and at international conferences. We further aim to disseminate our results to guideline committees.

Trial registration number: NCT01850719.

INTRODUCTION

Meniscal surgery is the most performed orthopaedic surgical intervention with over 41 000 procedures annually in the Netherlands.[1] In the USA, an increase of 49% was seen in arthroscopic partial meniscectomies (APMs) between 1996 and 2006. Half of these were performed in patients over 45 years old[2] and these numbers continue to rise since the proportion of population over 60 years will double from 11% to 22% between 2000 and 2050 (WHO). APM therefore contributes significantly to the costs of our healthcare system.

The quality of the menisci decreases with age and they become more vulnerable to damage and tears.[3–5] Both surgery and conservative treatment do not prevent the development of osteoarthritis (OA). APM in degenerative knees may even accelerate the process of OA more than a non-operative approach since more of the meniscus tissue is removed. However, to the best of our knowledge, no properly designed studies have been published investigating this hypothesis. The expected accelerated progression of OA after APM may influence the

number of knee arthroplasties subsequently needed. Faster progression to OA will lead to more patients on waiting lists for knee replacement and subsequently raise costs. In 2003, the National Hospital Discharge Survey in the USA described a total of 402 100 knee arthroplasties in that year and predicted this to grow by 673% to 3.48 million by 2030.[6] Preventing the accelerated progression of OA may result in stagnation of these numbers. Therefore, it could accomplish a substantial reduction of costs of healthcare usage.

Although arthroscopy for obstructive meniscal tears is widely accepted,[1 7] non-obstructive symptoms may not be triggered by the meniscal tear, but by early onset OA in middle-aged and older patients. Englund *et al*[8] identified a meniscal tear on MRI in 61% of nearly 1000 asymptomatic volunteers over 50 years old. APM in the non-obstructive meniscal tear group could therefore be seen as overtreatment since many are asymptomatic. Despite the wide use of APM for treatment of non-obstructive meniscal lesions, randomised controlled trials (RCTs) on this subject are sparse. Three recently published meta-analyses of 6–9 RCTs all found a small short-term benefit of surgery over conservative treatment, disappearing over time.[9–11] With these data and the lack of economic data, no recommendations can be made on a treatment of choice.

A meniscal tear could lead to knee OA, but knee OA could also lead to a meniscal tear.[12]

The main objective of this study is to evaluate the effectiveness and cost-effectiveness of surgical and conservative treatment, consisting of physical therapy (PT), of non-obstructive meniscal injuries in patients older than 45 years.

We hypothesise that meniscal tears are not a predominant factor causing knee symptoms in patients over 45 years and assume equal improvement of physical function in both groups and reduced costs with PT.

METHODS AND ANALYSIS

Study design

We will perform a multicentre RCT with an economic evaluation in the Netherlands. This trial was registered at clinicaltrials.gov (NCT01850719) and the Dutch Trial Registry (the Nederlands Trial Register; NTR3908) prior to the start of inclusion.

Setting

We included the first patient on 3 July 2013. We recruited patients at the orthopaedic outpatient clinic of nine hospitals, of which one was an academic hospital, in the Netherlands (Academic Medical Center Amsterdam, Diakonessenhuis Utrecht, OLVG Amsterdam, Medisch Centrum Alkmaar, Medisch Centrum Haaglanden Den Haag, Medisch Centrum Jan van Goyen Amsterdam, Sint Elisabeth hospital Tilburg, Slotervaart hospital Amsterdam, Tergooi hospital Hilversum). Eligible participants are randomised into two equal groups receiving either APM at the hospital of inclusion or PT. PT is performed at several preselected PT clinics in the area of the hospitals. These PT clinics are selected according to their qualifications and specific instructions regarding the protocol are provided prior to the start of the trial. Participants may prefer receiving treatment at another PT clinic. In these cases the researcher will contact these clinics prior to the start of the treatment to inform them about the study and provide them the PT protocol.

Participants

Participants between 45 and 70 years old with a symptomatic, non-obstructive, MRI-confirmed meniscal tear are being recruited at the outpatient clinic of the participating medical centres. Participants will be excluded when meeting one or more of the following exclusion criteria:

- Knee locking or trauma leading to acute surgery;
- Associated injuries on the index knee consisting of:
  - Symptomatic partial or total tear of the anterior cruciate ligament (ACL),
  - Posterior cruciate ligament tear,
  - OA of the knee, grade 4 on the Kellgren and Lawrence Grading Scale,
  - An injury to the lateral or posterolateral ligament complex with significant laxity;
- Previous knee surgery on the index knee (with the exception of diagnostic arthroscopy);
- Tumour that is suspected of malignancy, detectable on MRI;
- Obesity with a body mass index >35;
- American Society of Anesthesiologists (ASA) class 4 or 5 patients;
- General disease that effects physical function or systemic medication/abuse of steroids;
- Any other medical condition or treatment interfering with the completion or assessment of the trial, for example, contraindications to MRI or surgery;
- Drugs or alcohol abuse;
- Patients unable to fill out the Dutch questionnaires.

Participant recruitment

We will screen all patients with knee symptoms who visit the orthopaedic outpatient clinic for eligibility. Patients are informed verbally and in writing about the trial during their first visit. MRI will be conducted for confirmation of the diagnosis meniscal tear. Informed consent is signed when patients agree on participating in the trial at the second visit (on average after 7–14 days) for the result of the MRI.

Randomisation and blinding

After informed consent has been signed patients are randomly assigned to the treatment group (APM) or control group (PT). The randomisation is performed online using a computerised software program (TENALEA Clinical Trial Data Management system) in a 1:1 ratio using random blocks with a maximum block size of 6. Patients are stratified for centre and age (45–57 and 58–70 years old).

Interventions

Treatment group

APM is performed within 4 weeks after randomisation by the orthopaedic surgeons experienced in arthroscopic surgery, or orthopaedic residents skilled in arthroscopic surgery under supervision of an orthopaedic surgeon. Standardised surgery forms for this study are used including assessment of the lateral and medial menisci, the ACL, the level of chondropathy, and a general classification of the level of degeneration. After general or spinal anaesthesia, standard anteromedial and anterolateral portals were introduced for inspection of the knee joint. The affected meniscus is partially removed until a stable and solid meniscus is reached and all unstable and loose fragments are removed. All patients receive an information letter with perioperative instructions. Eight weeks after surgery (about 3 months after randomisation), patients visit the outpatient orthopaedic department for a postsurgery check-up. Considering that standard PT after APM has not been proven effective, patients are referred for PT in case of swelling or signs of atrophy, as advised by the Dutch Orthopaedic Association Guidelines.[1]

Control group

After randomisations, participants are referred to a PT clinic and the treatment on average starts within 1–2 weeks. The treatment protocol consists of a total of 16 sessions of 30 min (see online supplementary appendix A). Patients will visit the PT twice a week for 8 weeks. The PT programme consists of a progressive exercise programme and is based on the PT programme developed by Herrlin *et al*.[13] Three months after randomisation, the patients of the PT group visit the outpatient department to check for function and persistence of symptoms. Additionally, both groups receive the same home exercise instructions (see online supplementary appendix A).

Cross-over

Based on persistence of the symptoms, physical examination (PE) and the level of pain, the physician and participant will decide whether conservative treatment has been successful. When conservative treatment has failed, a delayed APM can be performed. This can be done during the entire follow-up time of the study.

Outcomes

Table 1 provides an overview of the outcomes at the different measurement moments.

Primary outcome

The primary outcome to evaluate the clinical effectiveness is the change in physical function from baseline to 2 years measured by the International Knee Documentation Committee (IKDC) 'Subjective Knee Form'. The IKDC is developed for knee-specific measurements of symptoms, function and sports activities in patients with ligament and meniscal injuries.[14] This self-administered questionnaire is validated for meniscal injuries[15 16] and consist of 19 questions. All items, except item 10a, are converted to a score with a maximum of 100 points, indicating no restrictions in daily and sports activities and the absence of symptoms. A difference of more than 8.8 points in IKDC score is considered clinically relevant.[16]

Secondary outcomes

The secondary outcomes to evaluate clinical effectiveness will be:

1. Change in:
   - A. General health, measured by RAND-36;[17]
   - B. Quality of life, measured by EuroQol 5 Dimensions 5 Level Survey (EQ-5D-5L);[18]
   - C. Pain, measured with the visual analogue scale in rest and during weight bearing;
   - D. Level of activity, measured by Tegner Activity Scale (TAS);[19]
     - a. Patient-specific complaints measured by the Patient Specific Complaints (PSC) questionnaire;[20]
   - E. Percentage of cross-overs; number of patients initially treated conservatively, treated secondarily by APM;
2. Progression of OA of the knee using the Kellgren and Lawrence score on X-rays;[21]
3. Relation between a participant's expectation of treatment and their satisfaction;
4. PE at baseline and 3 months, consisting of performance on physical tests (squatting with duck-walk, Thessaly test, McMurray), the range of motion, joint line tenderness and existence of joint effusion in the knee;
5. Adverse events including:
   - A. Minor: prolonged synovial fluid leakage from arthroscopy portals and bleeding;
   - B. Moderate: surgical site infection, vascular and neurological damage;
   - C. Severe: septic arthritis, cardiac events, pulmonary embolism and death.

Surgical instrument malfunction will be recorded, as well as reoperations including knee arthroplasties and rehospitalisation.

Sample size

Prior to the start of this trial, we calculated the initial sample size based on a power of 90%, an α of 0.05 and SD of 20 points (retrieved from the study of Crawford *et al*[15]). We used the previously mentioned clinically relevant difference of 8.8 points on the IKDC 'Subjective Knee Form', and to increase the power of our results, we rounded this down to a non-inferiority threshold of 8 points. We calculated that with 10% loss to follow-up after 24 months and 25% delayed APM in the PT group, 201 patients were needed per group in this non-inferiority trial. This meant a total of 402 patients. The

Table 1 Measurement moments

Baseline (t0)	3 months (t2)	6 months (t3)	9 months (t4)	12 months (t5)	18 months (t6)	24 months (t7)
CRF-1	CRF-2	CRF-3	CRF-4	CRF-5	CRF-6	CRF-7
Visit						
IKDC	IKDC	IKDC		IKDC		IKDC
RAND-36	RAND-36	RAND-36		RAND-36		RAND-36
EQ-5D-5L	EQ-5D-5L	EQ-5D-5L	EQ-5D-5L	EQ-5D-5L	EQ-5D-5L	EQ-5D-5L
VAS	VAS	VAS		VAS		VAS
TAS	TAS	TAS		TAS		TAS
PSC	PSC	PSC		PSC		PSC
TiC-P	TiC-P	TiC-P	TiC-P	TiC-P	TiC-P	TiC-P
PE	PE					
X-ray						X-ray
Expectation	Satisfaction	Satisfaction		Satisfaction		Satisfaction
MRI						

CRF, Case Report Form; EQ-5D-5L, EuroQol 5 Dimensions 5 Level Survey; IKDC, International Knee Documentation Committee; PE, physical examination; PSC, Patient Specific Complaints questionnaire; TAS, Tegner Activity Scale; TiC-P, Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness; VAS, visual analogue scale.

sample size was calculated for the intention-to-treat analysis.

In order to avoid unnecessary inclusions and unnecessary delay, we recalculated our SD halfway through the study. This interim analysis was performed by an independent committee consisting of an orthopaedic surgeon/expert in the field and an orthopaedic research coordinator/statistical expert. Only the SD was recalculated, all other outcome data remained blinded and no analyses were performed for any of the outcomes with different sample sizes. With an SD of 18 points (compared to the SD of 20 in our initial calculation) the committee recalculated the sample size. We agreed on a sample size reduction to a total number of 320 patients (160 per group). The Ethics Review Board granted approval for this on 27 October 2015. The change of sample size has been updated in the trial registries.

Data analysis

Effectiveness analysis

To investigate the clinical effectiveness of both treatment groups, we will use linear mixed-model analysis for continuous outcomes. Logistic generalised estimation equation analysis will be used for dichotomous outcomes. This method takes into account the dependency of observations within a patient, and the fact that not all patients may be assessed at each time point (missing data). All analyses will be carried out on an intention-to-treat and per/protocol basis, as well as cross-over analysis.

In the primary linear mixed model, the outcome variable studied (eg, physical function on the IKDC) will be analysed as a dependent variable. To investigate the effect at the different time points, we will analyse the model, according to a four-level structure (treatment group, centre, patient and time, in which time will be treated as a categorical variable to assess the treatment effects at the different time points). Time will be included as a dummy variable (reference is baseline T0), and four interaction terms will be analysed (T2Xgroup; T3Xgroup; T5Xgroup; T7Xgroup). To investigate the overall effect of both treatments (irrespective of time), we will also analyse the model according to a three-level structure (treatment group, centre, patient). The baseline outcome will be included as a covariate in all models.

Besides analysing the basic model (eg, analysis of main effects for treatment group and time and a time-by-treatment interaction), we will also control for possible confounders, by adding them as covariates (eg, body mass index, gender, profession, ASA classification, the affected meniscus, the type of tear and the status of OA according to Kellgren and Lawrence Grading Scale for Osteoarthritis). Covariates are defined as resulting in more than 10% change in the parameter estimate of time-by-treatment interaction.

In the secondary linear mixed models, the outcome variables studied (eg, general health on the RAND-36, quality of life on the EQ-5D-5L, level of activity on the TAS, knee pain on the question 10 of IKDC, the correlation between a patient's expectation and satisfaction, productivity losses on the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P), muscle strength, range of motion and squatting) will be analysed in a similar way.

The estimated main effects for treatment at different assessment points under these different models are reported as in differences in means with 95% CIs for continuous outcomes, and ORs with 95% CIs for dichotomous outcomes

At the time points 3 months (T2), 6 months (T3), 12 months (T5) and 2 years (T7), we will describe the incidence of revisions (intervention group) or treatment failures (=delayed APM, control group) using descriptives.

After 2 years (T7), we will compare the incidence of development or progression of OA between groups using a χ^2 test (or Fisher's exact as appropriate).

For all analyses, a two-tailed value of p<0.05 is considered to be significant.

We will consult a statistician for all longitudinal analysis.

Cost-effectiveness analysis

General considerations

The economic evaluation will be conducted from a societal perspective. The aim of the economic evaluation is to measure, value and analyse total costs of patients in both groups and to relate the difference in costs between the two treatment groups to the difference in clinical effects. We will perform both a cost-effectiveness and cost-utility analysis. The time horizon of the economic evaluation is 24 months, so discounting will be used. Sensitivity analysis will be performed to assess the robustness of the results using different assumptions regarding costs and effects.

Patient outcome analysis

Effect measures in the economic evaluation are physical function, pain intensity and general health. Quality-adjusted life-years (QALYs) based on the Dutch tariff for the EuroQol will also be measured.[22 23]

The analysis will be carried out according to the intention-to-treat principle. Missing cost and effect data will be imputed using multiple imputations according to the National Institute for Health and Care Excellence (NICE) algorithm developed by van Buuren *et al*.[24]

We will perform a full cost-effectiveness and cost-utility analysis. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs between the treatment groups by the difference in mean effects.

Bias-corrected and accelerated bootstrapping with 5000 replications will be used to estimate 95% CIs around cost differences and the uncertainty surrounding the ICERs. Rubin's rules will be used to pool the results from the different multiple imputed data sets. Uncertainty surrounding the ICERs will be graphically presented on cost-effectiveness planes.

Cost-effectiveness acceptability curves will also be estimated using the net benefit framework.[25] Cost-effectiveness acceptability curves show the probability that APM is cost-effective compared with PT for a range of different ceiling ratios thereby showing decision uncertainty.[26]

Cost-analysis

Costs will be measured using a web-based questionnaires, which is a modified version of the TiC-P.[27] Direct costs include costs of APM surgery and costs of PT, but also other healthcare expenses for knee problems such as general practitioner care, costs of visits to other primary care providers, ambulatory and inpatient hospital care, medication and home care. Indirect costs include absenteeism from paid and unpaid work and presenteeism. The friction cost approach will be used in the primary analysis to estimate indirect costs.[28] We will use standard prices published in the Dutch costing guidelines for the valuation of healthcare usage.[29] Medication use will be valued using prices of the Royal Dutch Society for Pharmacy.

Cost-effectiveness analysis

Effect measures in the economic evaluation are physical function based on the IKDC 'Subjective Knee Form' and general health based on the EuroQol. QALYs based on the Dutch tariff for the EuroQol will also be measured.[22 23]

The analysis will be carried out according to the intention-to-treat principle. Missing cost and effect data will be imputed using multiple imputations according to the NICE algorithm developed by van Buuren *et al*.[24]

We will perform a full cost-effectiveness and cost-utility analysis. ICERs will be calculated by dividing the difference in mean total costs between the treatment groups by the difference in mean effects. Bias-corrected and accelerated bootstrapping with 5000 replications will be used to estimate 95% CIs around cost differences and the uncertainty surrounding the ICERs. Rubin's rules will be used to pool the results from the different multiple imputed datasets. Uncertainty surrounding the ICERs will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves will also be estimated using the net benefit framework.[25] Cost-effectiveness acceptability curves show the probability that APM is cost-effective compared with PT for a range of different ceiling ratios thereby showing decision uncertainty.[26]

Budget impact analysis

General considerations

In the budget impact analysis, the results of the economic evaluation will be linearly extrapolated over a period of 5 years to estimate the financial consequences of implementation of the study results. An estimate of the long-term financial consequences will also be given to quantify the impact of the expected decrease of the progression of OA and therefore the number of knee arthroplasties. The intervention will be offered to patients aged 45–70 years who were diagnosed with symptomatic, non-obstructive, MRI-confirmed meniscal tears. Perspectives that will be considered are the societal, government (Budget Kader Zorg) and insurer. Different scenarios will be evaluated including the following: (1) all patients will receive APM; (2) all patients will receive PT; (3) PT will replace APM gradually over a period of 4 years (25% change per year).

One-way sensitivity analysis will be performed in which the change rate per year and the reduction of number of knee arthroplasties will be varied.

Cost-analysis

The total number of patients aged 45–70 years who were diagnosed with symptomatic, non-obstructive, MRI-confirmed meniscal tears will be estimated based on Dutch incidence and prevalence rates. Resource usage is calculated by multiplying the number of eligible

patients with the resource usage rates obtained from the cost-effectiveness analysis.

We will use different prices to value resource use depending on the perspective of the analysis: Dutch standard costs for the societal perspective, actual Nederlandse Zorgautoriteit (in English: Dutch Healthcare Authority) (NZA) tariffs for the government perspective, and average tariffs NZA for the insurer perspective.

Both resource use and annual costs will be presented over a 5-year period for all perspectives. Aggregated and disaggregated total costs per year will be presented for the different perspectives and scenarios. For the long-term analysis, total costs over the whole time horizon will be estimated.

Data analysts are blinded to the type of treatment by numerical coding of the performed intervention. After finalising data analysis, this code will be broken for publication purposes.

Data handling and confidentiality

Data will be collected using online questionnaires. All participant data will be anonymised by assigning study numbers to each participant. The study numbers will not be based on the patient initials or birth date. The key to these study numbers is only available to the researchers (JCAN and on demand by the principal investigators). Outcome data, anonymised, is only accessible for the coordinating investigator (VVvdG), principal investigators (RWP and AdG), research assistant (JCAN), statistical analysers (NW and VABS) and authorised research personnel of the Joint Research Group at the OLVG Amsterdam. Data will be collected and stored for a period of 15 years. Paper and original questionnaires will be kept in a database at the initiating hospital (OLVG). Data will be processed and stored in SPSS, password protected.

Security requirements: Data input capabilities are limited to the coordinating investigator (VAvdG) and the research assistant (JCAN). Data processing capabilities are limited to the coordinating investigator, statistical analysers (NW and VABS), the principal investigators, and authorised research staff.

The handling of personal data will comply with the Dutch Personal Data Protection Act (de Wet Bescherming Persoonsgegevens, Wbp).

Steering and data monitoring committee

There is no official steering committee for this study. The following representatives from the participating organisations are involved in the project oversight and control: RWP, MD PhD (principal investigator and sponsor); VAvdG, MD; NW, PhD; VABS PhD; MWvT, PhD; and JCAN, Msc.

All study related problems or (serious) adverse events (SAEs) will be discussed with the principal investigator RWP, and researchers VAvdG, VABS and JCAN. SAEs will be officially reported to the ethical committee. The ethical committee judges will decide whether the safety of the patients is jeopardised and whether the trial can be continued or not.

There is no official data monitoring committee. Data entry will be performed by one of the researchers (JCAN) and checked and cleaned according to the quality handbook of the EMGO+ institute for health and care research (http://www.emgo.nl/kc). In addition, a random sample of 5% of the data will be re-entered by another researcher to check for inconsistencies. A third researcher will be involved with the data processing and analysis, which will be performed without having knowledge of the allocation key. All data analyses will be discussed with the researchers (RWP, VAvdG and JCAN) before the final presentation of the results. A professor (MWvT) specialised in cost-effectiveness will perform the economic evaluation in association with one of the researchers (VAvdG).

Ethics and dissemination

This study will be conducted in accordance with the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO). Also, all institutional review boards have approved the start of the study. All substantial amendments to the protocol will be notified to the ethics committee and to the competent authority. Non-substantial amendments will not be notified to the accredited Medisch Ethische ToetsingsCommissie (in English Medical Ethical Committee) (METC) and the competent authority, but will be recorded and filed by the sponsor. Written informed consent will be obtained from all participating patients. The research coordinator will report all SAEs within 24 hours of noticing, using the online submission system of the ethics committee. The ethical committee judges will decide whether the safety of the patients is jeopardised and whether the trial can be continued or not. We will submit our study results for publication in peer-reviewed journals and present at international conferences. Furthermore, we aim to disseminate our results to guideline committees.

DISCUSSION

In this protocol paper, we propose the protocol of an economic evaluation study for the assessment of (cost-) effectiveness of early APM versus conservative treatment with optional delayed meniscectomy for patients between 45 and 70 years old with a meniscal tear. Previous RCTs[7 13 30–33] found no difference in outcome between surgical and conservative treatment.

Since we were unaware of the exact SD of the IKDC in this patient group, we decided to calculate the SD in our own group. Subsequently, we could use this for a recalculation of our sample size in order to avoid unnecessary inclusions and any further (unnecessary) delay. The SD in our own group was found to be 18, compared with the SD of 20 used for our initial sample size

calculation. This resulted in a reduction of 82 patients. As previously mentioned, an independent committee consisting of an orthopaedic surgeon/expert in the field and an orthopaedic research coordinator/statistical expert were appointed for this recalculation. During this process, all other data remained blinded and no analyses were performed for any of the outcomes with different sample sizes. The Ethics Review Board approved this recalculation.

This RCT will be the first to investigate and publish data on cost-effectiveness of both treatment groups in this specific group of patients. Therefore, this trial adds to the clinical evidence of treatment of meniscal tears which contributes to the ongoing debate to reduce healthcare costs in the western world.

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Contributors All authors have contributed to the design of this trial protocol. VAvdG, VABS, NW, AdG, Eduard LAM Mutsaerts, DBFS and RWP have contributed to writing this manuscript. VAvdG, VABS, RWP and MWvT have contributed to the statistical part. MWvT has written the part on the economic evaluation. RWP is the principal investigator for this trial. CN has designed and written the PT protocol. VAvdG and JCAN have rewritten the protocol to the current version for publication. All authors, and all collaborators in the research group, have contributed to the manuscript and read and approved the final manuscript.

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Competing interests None declared.

Ethics approval The Ethical Review Board (Medical Research Ethics Committees United (MEC-U), Nieuwegein, the Netherlands) gave approval for the start of this trial on 20 June 2013, file number NL44188.100.13.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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